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ORGANIC SYNTHESES

AN ANNUAL PUBLICATION OF SATISFACTORY METHODS FOR THE PREPARATION OF ORGANIC CHEMICALS

Volume 50
1970

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"John Wiley & Sons, Inc. is pleased to publish this volume of Organic Syntheses on behalf of Organic Syntheses, Inc. Although Organic Syntheses, Inc. has assured us that each preparation contained in this volume has been tested by two independent laboratories and that any hazards that may be uncovered are clearly set forth in the write-up of each preparation, John Wiley & Sons, Inc. does not warrant the preparations against any safety hazards and assumes no liability with respect to the use of the preparations."

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NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds that are of general interest, as well as procedures that illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the range of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point range should be reported, and for each liquid product the range of boiling point and refractive index should be included. In most instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, mass, or nuclear magnetic resonance spectra, and criteria of purity such as gas chromatographic data. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where standard commercial grades are specified.

Beginning with Volume 49, Sec. 3., Methods of Preparation,

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and Sec. 4., Merits of the Preparation, have been combined into a single new Sec. 3., Discussion. In this section should be described other practical methods for accomplishing the purpose of the procedure that have appeared in the literature. It is unnecessary to mention methods that have been published but are of no practical synthetic value. Those features of the procedure that recommend it for publication in *Organic Syntheses* should be cited (synthetic method of considerable scope, specific compound of interest not likely to be made available commercially, method that gives better yield or is less laborious than other methods, etc.). If possible, a brief discussion of the scope and limitations of the procedure as applied to other examples as well as a comparison of the method with the other methods cited should be included. If necessary to the understanding or use of the method for related syntheses, a brief discussion of the mechanism may be placed in this section. The present emphasis of *Organic Syntheses* is on model procedures rather than on specific compounds (although the latter are still welcomed), and the Discussion section should be written to help the reader decide whether and how to use the procedure in his own research. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparations that are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

FIFTY YEARS OF ORGANIC SYNTHESES

The genesis of *Organic Syntheses* coincided with the initiation of a rapid development of the organic chemical industry in the United States. Prior to the advent of World War I the investigator in the field of organic chemistry depended for his supply of chemicals and reagents primarily on the German chemical concern of Kahlbaum. This company distributed throughout the world, either directly or through supply houses, a large variety of chemicals and reagents in various sized containers.

The British blockade of German shipping in 1914 resulted in the stoppage of importation of German chemicals. The supply of chemicals still in storage in the United States was soon exhausted. The investigator was thus faced with the necessity of devoting valuable research time to the preparation of his previously purchased raw materials.

No satisfactory directions were available for the preparation of such compounds. This situation induced Hans T. Clarke, James B. Conant, and me, while together at a Chemical Society Meeting, to discuss the possibility of publishing a series of annual volumes of preparations of organic compounds. The preparations would be described in such detail that they could, if carefully followed, be readily duplicated by a student. The novel feature was adopted that each preparation before publication must be checked in the laboratory of an editor and always in a laboratory other than that of the contributor. When the decision was made to proceed, Oliver Kamm of Parke Davis and Company was invited to join in the formation of the original editorial board.

A description of the plan and those of several preparations in finished form were submitted in succession to three different publishers, each of which declined acceptance. This was discouraging. It seemed incredible to the editors that the publishing concerns should show so little interest, since the probably low profits of such a publication would be offset by the fringe benefit of closer acquaintance with the current and future editors who might be potential authors of more profitable books. It then came to light that each publisher had sent the manuscript to the same referee who had decidedly unfavorable comments.

Mr. E. P. Hamilton of John Wiley and Sons happened into my office about this time. The manuscript was submitted to him with the proviso that the referee to be selected should not be the one who had already expressed his opinion three times. Soon after, John Wiley and Sons agreed to be the publisher and the first volume of *Organic Syntheses* appeared in 1921.

Following the appearance of the first two or three volumes more editors were added gradually until the total reached nine or ten, a number that has been maintained ever since. When ten volumes had appeared, the policy was established that each member of the editorial board from then on would serve seven years, one of which would be as editor-in-chief of a volume. He would then become a member of the Advisory Board and an Active Editor would be elected in his place. This policy is still in effect. A Secretary to the Board was appointed whose term of office was unspecified; each has served ten years or more.

The nature of the preparations in *Organic Syntheses* has changed with the years. In the 1920s and 1930s as the organic chemical industry in the United States expanded, the preparations selected were of more complex compounds. Emphasis was placed on preparations involving new techniques and procedures that might have wider application.

At the close of World War I, the Eastman Kodak Company established a division for production of research chemicals. One or two other concerns of lesser significance entered the same field some time later. Several years after World War II, however, additional concerns began marketing such chemicals. This situation induced the Active Board of Organic Syntheses to devote more effort to uncovering preparations involving new and improved procedures.

With more and more chemicals available from industry, the future program of *Organic Syntheses* required consideration. The Active Board came to the wise conclusion that a change must be made in the general character of the preparations, if the publication was to be of continuing value to the research chemist. It was decided that preparations exemplifying new and general types of compounds, involving novel reagents and reactions, would be most acceptable. This plan was initiated first in Volume 41, edited by John D. Roberts; this and succeeding volumes have demonstrated the utility of such preparations to the needs and current developments of organic chemistry.

The standard presentation of each preparation from the start was under the following headings: (1) Procedure, (2) Notes, and (3) Methods of Preparation. To these was added in the volumes published during the past ten years a desirable fourth heading, Merits of the Method, which explains why the method was deemed worthy of publication. Spectroscopic data, such as UV, IR, and NMR, have been added where pertinent.

The Collective Volumes containing in revised form and in logical order the preparations appearing in the previous ten annual volumes have been published every ten years. Several indices have been incorporated in the decennial publications so that the investigator may locate with a minimum of search a particular compound, a type of reaction, or a reagent. The fifth decennial volume is now being assembled.

It would be futile to attempt to forecast what the research chemist will require most in the future. It is reasonable to assume that the content of *Organic Syntheses* can be adjusted from time to time to be of continuing value to the current demands of the investigator in the field of organic chemistry.

May 7, 1970 ROGER ADAMS

EDITOR'S PREFACE

The appearance of this Golden Anniversary Volume of *Organic Syntheses* testifies to the continued importance of synthesis in our science, and to the continued need for well-described and checked procedures for carrying out synthetic reactions. Whereas in the early years *Organic Syntheses* served the critical function of providing directions for the preparation of useful specific compounds, in modern times the emphasis has changed. Recent volumes stress model procedures which illustrate important types of reactions, and attention is paid to the generality of the procedure as well as to the interest of the particular example which is described. The current volume continues this trend, and in many of these "preparations" the general reaction which is illustrated is of more importance than the specific compound which results.

Thus β-PHENYLCINNAMALDEHYDE illustrates the use of the Schiff base of an aldehyde to direct a mixed aldol condensation, while 2,2-DIMETHYL-4-PHENYLBUTYRIC ACID involves alkylation of the lithium enolate of a carboxylate ion. The use of cyclooctatetraene as a source of four carbons in sequences terminating in a reverse Diels-Alder reaction is illustrated in *cis*-3,4-DICHLOROCYCLOBUTENE and in *trans,trans*-1,4-DIACETOXYBUTADIENE, while in DIETHYL *trans*-Δ^4-TETRAHYDROPHTHALATE sulfolene is used, in a Diels-Alder reaction, as a more convenient equivalent of 1,3-butadiene.

Several of the examples involve the use of metals. Thus copper(I) is used in DIETHYL *tert*-BUTYLMALONATE to induce 1,4 addition of a Grignard reagent to an unsaturated ester, in 1-PHENYL-1,4-PENTADIYNE to promote coupling of a Grignard reagent with a halide, and in 2,2′-DITHIENYL SULFIDE to catalyze displacement of an aryl halogen. N,N-DIMETHYLDODECYLAMINE OXIDE produces an anhydrous amine oxide by oxidation using a vanadium catalyst, while in *cis*-4-*tert*-BUTYLCYCLOHEXANOL an iridium catalyst is used to hydrogenate a cyclohexanone to the axial alcohol. An aromatic ring is partially reduced with sodium amalgam in *trans*-1,2-DIHYDROPHTHALIC ACID, and with lithium and ethylamine in $\Delta^{9,10}$-OCTALIN.

A useful modification of the Arndt-Eistert reaction is used in ETHYL 1-NAPHTHYLACETATE, while a general procedure for the preparation of hydrazones free of azines is described in ACETOPHENONE HYDRAZONE. Two ways to use chlorosulfonyl isocyanate in the preparation of nitriles are illustrated in CINNAMONITRILE and 2,4-DIMETHOXYBENZONITRILE, while 1-NITROCYCLOOCTENE involves the use of N_2O_4 to convert an olefin to the nitro-olefin. α,α'-DIBROMODIBENZOSULFONE illustrates two general procedures for preparing α-halosulfones, 2-THIOPHENE THIOL involves direct metallation of thiophene, and *cis*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID utilizes selective ester hydrolysis to separate the *cis*, *trans* mixture.

Convenient syntheses are also described for compounds of utility or importance, such as the useful oxidizing agent *m*-CHLOROPERBENZOIC ACID and the versatile formylating agent ACETIC FORMIC ANHYDRIDE. 1,3-DITHIANE is an intermediate in some novel aldehyde and ketone syntheses, *t*-BUTYL AZIDOFORMATE is useful for the protection of amino groups, and TRIMETHYLSILYL AZIDE is a convenient, and stable, substitute for hydrazoic acid in some reactions. The preparation of highly reactive 2-DIAZOPROPANE and its perfluoro derivative, BIS(TRIFLUOROMETHYL)DIAZOMETHANE, are described, as are the theoretically important CYCLOBUTADIENEIRON TRICARBONYL and 2,3-DIPHENYLVINYLENE SULFONE. 2,3-DIPHENYL-1,3-BUTADIENE is prepared by an unusual new reaction.

The members of the Editorial Board take this opportunity to thank the contributors of preparations. They welcome suggestions of changes that would improve the usefulness of *Organic Syntheses*. The attention of submitters of preparations is particularly drawn to the instructions on pages v and vi, which reflect changes introduced in the preceding volume. In addition, this and future volumes of *Organic Syntheses* will contain an insert listing all preparations which have been received during the preceding year. These are available from the Secretary's office, prior to checking, for a nominal fee. In this way, we hope to make preparations more quickly available, and to gain further information concerning the types of preparations found valuable by users of *Organic Syntheses*. All procedures will, of course, continue to be checked before final publication.

RONALD BRESLOW

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ORGANIC SYNTHESES

ACETIC FORMIC ANHYDRIDE

(Acetic acid, anhydride with formic acid)

$CH_3COCl + HCOONa \rightarrow CH_3COOCHO + NaCl$

Submitted by LEWIS I. KRIMEN[1]
Checked by JAMES SAVAGE and PETER YATES

1. Procedure

A dry 2-l. three-necked round-bottomed flask equipped with a stirrer, a thermometer, a reflux condenser with calcium chloride tube, and a dropping funnel is charged with 300 g. (4.41 moles) of sodium formate (Note 1) and 250 ml. of anhydrous ether (Note 2). To this stirred mixture is added 294 g. (266 ml., 3.75 moles) of acetyl chloride (Note 3) as rapidly as possible, while the temperature is maintained at 23–27° (Note 4). After the addition is complete, the mixture is stirred for 5.5 hours at 23–27° to ensure complete reaction. The mixture is then filtered with suction, the solid residue is rinsed with 100 ml. of ether, and the washings are added to the original filtrate (Note 5). The ether is removed by distillation at reduced pressure, and the residue is distilled to yield 212 g. (64%) of colorless acetic formic anhydride, b.p. 27–28° (10 mm.), 38–38.5° (39 mm.); $n^{20}\text{D}$ 1.388 (Note 6).

2. Notes

1. Reagent grade sodium formate from J. T. Baker Chemical Co. was used; it was finely ground to ensure better contact. It is imperative that extreme care be taken to ensure anhydrous conditions throughout the procedure, since hydrolysis produces formic and acetic acids, which are very difficult to remove from the product. A slight excess of sodium formate ensures a product free of acetyl chloride.

2. Mallinckrodt AR grade ether was used without further drying by the submitter. The checkers, working at half scale, found it essential to dry the ether over sodium.

3. Acetyl chloride from Matheson, Coleman and Bell was used without further purification.

4. The addition of acetyl chloride is mildly exothermic; the exotherm can be controlled by slower addition or by the use of a cooling bath (20–24°). The addition is completed in *ca.* 5 minutes.

5. The filtration and subsequent ether rinse should be carried out quickly in order to keep the filtrate dry.

6. The acetic formic anhydride may be stored at 4° in a standard-taper round-bottomed flask fitted with a polyethylene stopper. Moisture catalyzes the decomposition of the product to acetic acid with the evolution of carbon monoxide. *The material must not be stored in sealed containers!*

7. The infrared spectrum of neat acetic formic anhydride shows two bands in the carbonyl region at 1765 and 1791 cm.$^{-1}$ and carbon-oxygen-carbon stretching absorption at 1050 cm.$^{-1}$ (a band at 1180 cm.$^{-1}$ could also be due to C—O—C). The n.m.r. spectrum (neat, tetramethylsilane as an internal standard) shows a singlet at δ 2.25 (acetyl protons) and a singlet at δ 9.05 (formyl proton). If the product is not pure, the following peaks may also be observed: δ 2.05 (CH_3CO_2H), 2.20 [$(CH_3CO)_2O$], 2.68 (CH_3COCl), 8.05 ($HCOOH$), 8.85 [$(HCO)_2O$]. The spectrum of the product obtained by the checkers showed slight contamination with acetic anhydride and formic anhydride.

3. Discussion

Acetic formic anhydride has been prepared by the reaction of formic acid with acetic anhydride[2,3] and ketene,[4,5] and of acetyl chloride with sodium formate.[6] The present procedure is essentially that of Muramatsu.[6] It is simpler than others previously described and gives better yields. It is easily adapted to the preparation of large quantities, usually with an increase in yield. Acetic formic anhydride is a useful intermediate for the formylation of amines,[3,7] amino acids,[8,9] and alcohols,[2,10] for the synthesis of aldehydes from Grignard reagents,[11] and for the preparation of formyl fluoride.[12]

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ACETONE HYDRAZONE

$$CH_3COCH_3 \xrightarrow{N_2H_4 \cdot H_2O} (CH_3)_2C{=}NN{=}C(CH_3)_2 \xrightarrow{N_2H_4} (CH_3)_2C{=}NNH_2$$

Submitted by A. C. DAY[1] and M. C. WHITING[2]
Checked by G. SWIFT and W. D. EMMONS

1. Procedure

Caution! Hydrazine is toxic and should be handled in a hood. Anhydrous hydrazine is extremely reactive with oxidizing agents (including air) and should always be prepared and used behind a protective screen.

A. *Acetone azine.* In a 500-ml. round-bottomed flask fitted with a mechanical stirrer (Note 1) and dropping funnel is placed 145 g. (183 ml., 2.5 moles) of acetone (Note 2). The flask is cooled in an ice bath and, with vigorous stirring, 65.5 g. (1.31 moles) of 100% hydrazine hydrate (Note 2) is added at such a rate that the temperature is maintained below 35° by the ice bath. The addition takes 20–30 minutes. The mixture is stirred for an additional 10–15 minutes, and then 50 g. of potassium hydroxide pellets is added with vigorous stirring and continued cooling (Note 3). The upper liquid layer is separated and allowed to stand over 25 g. of potassium hydroxide pellets for 30 minutes with occasional swirling (Note 4). After filtration, the liquid is further dried with two successive 12.5-g. portions of potassium hydroxide. Distillation then gives 120–126 g. (86–90%) of almost colorless acetone azine, b.p. 128–131°, n^{22}D 1.4538 (Note 5).

B. *Acetone hydrazone.* Anhydrous hydrazine is prepared by heating under reflux 100% hydrazine hydrate with an equal weight of sodium hydroxide pellets for 2 hours, followed by distillation in a slow stream of nitrogen introduced through a capillary leak. (*Caution! Distillation in air can lead to explosion.*) The distillate boils at 114–116° and the yield is 95–97% (Note 6).

A mixture of 112 g. (1.0 mole) of acetone azine and 32 g. (1.0 mole) of anhydrous hydrazine is placed in a 300-ml. round-bottomed flask fitted with a reflux air condenser and drying tube, and kept at 100° for 12–16 hours. (*Caution! This reaction and the subsequent distillation should be carried out behind a protective screen.*) The crude product is then rapidly distilled through a water-cooled condenser and the colorless fraction boiling at 122–126° collected, n^{22}D 1.4607 (Note 7). It weighs 111–127 g. (77–88%, Notes 7 and 8) and is essentially pure acetone hydrazone (Note 9).

2. Notes

1. A Hershberg stirrer made of Nichrome wire is the most efficient for aiding dissolution of the potassium hydroxide added after azine formation is complete.

2. The acetone and hydrazine hydrate were good-quality commercial products used with purification.

3. The dissolution of the potassium hydroxide is strongly exothermic. A small proportion may remain undissolved.

4. A lower, aqueous phase may form at this stage. The product is easily decanted from it.

5. The distillation gives a small forerun, b.p. 120–128°, containing hydrazine and acetone hydrazone. There is virtually no distillation residue. The submitters carried out the preparation of both acetone azine and acetone hydrazone on a fourfold scale with comparable results.

6. The purity is 95–98% by this method.[3] The purity is lower (85–95%) by an alternative procedure[4] which requires separation of the hydrazine and alkaline phases above 60°; with the latter method the submitters found that a frequent problem

was the solidification of the lower phase in the separating funnel, and in one case *a very serious fire* occurred during transference of the hot (*ca.* 100°) mixture to the separating funnel.

7. The forerun contains hydrazine. Material boiling above 126° contains much acetone azine. With a slow rate of distillation, disproportionation occurs and the yield of acetone hydrazone is reduced. If the forerun and material boiling above 126° are combined and reheated at 100° for 12–16 hours, they give more acetone hydrazone on redistillation. With further repetitions of this procedure, the yield is almost quantitative.

8. The highest yields were obtained in cases where the anhydrous hydrazine was treated with barium oxide for several hours before use.

9. The hydrazone should be used as soon as possible. If it is stored, care must be taken to exclude moisture, which catalyzes disproportionation to hydrazine and acetone azine.[5–7] Even in the absence of moisture it disproportionates slowly at room temperature and so should be redistilled immediately before use. Old samples can be regenerated fairly satisfactorily by reheating them for 12–16 hours at 100° before redistillation, but there is always some irreversible decomposition to high-boiling products during storage.

3. Discussion

The procedure for acetone azine is essentially that of Curtius and Thun.[5] The method for acetone hydrazone is adapted from that of Staudinger and Gaule.[8] The hydrazone has been prepared directly from acetone and hydrazine, but this is much less satisfactory.[6]

Acetone hydrazone is produced in good yield by the method described, and inferior product is obtained without the precautions noted. The compound is used for the preparation of 2-diazopropane.[8–10]

[1] Dyson Perrins Laboratory, Oxford University, England.

[2] Department of Organic Chemistry, University of Bristol, England.

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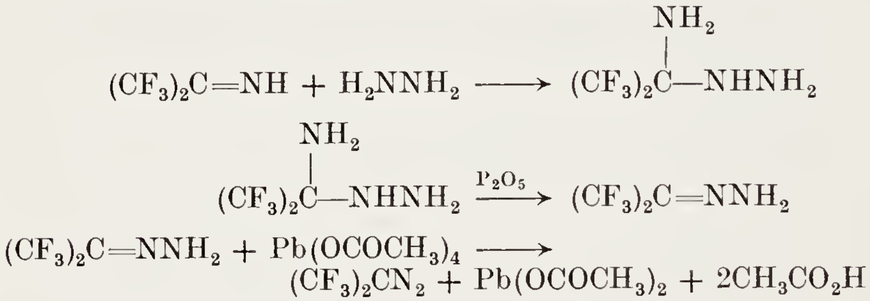
BIS(TRIFLUOROMETHYL)DIAZOMETHANE



$$(CF_3)_2C{=}NH + H_2NNH_2 \longrightarrow (CF_3)_2\overset{\displaystyle NH_2}{\overset{|}{C}}{—}NHNH_2$$

$$(CF_3)_2\overset{\displaystyle NH_2}{\overset{|}{C}}{—}NHNH_2 \xrightarrow{P_2O_5} (CF_3)_2C{=}NNH_2$$

$$(CF_3)_2C{=}NNH_2 + Pb(OCOCH_3)_4 \longrightarrow (CF_3)_2CN_2 + Pb(OCOCH_3)_2 + 2CH_3CO_2H$$

Submitted by W. J. Middleton and D. M. Gale[1]
Checked by L. Scerbo and W. D. Emmons

1. Procedure

Caution! This procedure should be carried out in a good hood and behind a shield to avoid exposure to the toxic compounds, hexafluoroacetone imine and hydrazine.

A. *Hexafluoroacetone hydrazone.* A 100-ml. three-necked round-bottomed flask fitted with a thermometer, a gas inlet tube, and a Dewar condenser and containing a magnetic stirring bar is charged with 16 g. (0.5 mole) of anhydrous hydrazine[2] and cooled in an ice-methanol bath. The condenser is filled with a cooling mixture of ice and methanol, the magnetic stirrer is started, and 82.5 g. (0.5 mole) (Note 1) of hexafluoroacetone imine[3] is slowly distilled into the flask through the gas inlet tube, while the temperature is maintained below 10°. After the addition, which requires about 1 hour, the cooling bath is removed and the reaction mixture is allowed to warm to room temperature and is then poured rapidly into a 500-ml. single-necked round-bottomed flask containing 150 g. of phosphorus pentoxide. A spatula is used to partially mix the liquid with the phosphorus pentoxide (Note 2), and then the flask is quickly fitted with a simple still head with condenser and heated by means of a heating mantle until no further distillation occurs (Note 3). The crude distillate is redistilled through a 45-cm. spinning-band column to give 48–53 g. (53–59% conversion) of hexafluoroacetone hydrazone as a colorless liquid, b.p. 95.5–96°, $n^{25}\text{D}$ 1.3298.

B. *Bis(trifluoromethyl)diazomethane.* A 1-l. three-necked round-bottomed flask is equipped with a sealed mechanical stirrer and a 100-ml. pressure-equalizing dropping funnel. The third neck is connected by means of pressure tubing to a 50-ml. capacity cold trap immersed in a dry ice-acetone cooling bath and protected from the atmosphere with a calcium chloride drying tube. The system is purged with nitrogen, and 375 ml. of benzonitrile and 120 g. (0.27 mole) of lead tetraacetate (Note 4) are placed in the flask. Stirring is started and the flask is cooled by means of an ice bath. A solution of 45 g. (0.25 mole) of hexafluoroacetone hydrazone in 50 ml. of benzonitrile is added by means of the dropping funnel over a period of 1 hour. The ice bath is removed and the reaction mixture is stirred for an additional hour at room temperature. During this time some product collects in the cold trap. The remaining product is distilled into the trap at 10 mm. pressure by removing the drying tube and connecting the trap to a pump or aspirator. A small amount of acetic acid and other impurities can be removed by trap-to-trap distillation. There is obtained 20–21 ml. or 34–35 g. (76–79%) (Note 5) of bis(trifluoromethyl)-diazomethane as a yellow liquid, b.p. 12–13°. The product is neither impact- nor static-sensitive (Note 6) and is stable to long storage at −78°; however, it partly decomposes with loss of nitrogen after several weeks at room temperature.

2. Notes

1. If it is inconvenient to distill the hexafluoroacetone imine directly from a cylinder, it may be condensed first in a calibrated cold trap cooled to −10° and then distilled from the trap into

the reaction mixture. About 55 ml. of the imine, measured at −10°, is 0.5 mole.

2. *Caution! A spontaneous reaction may result if mixing is prolonged beyond 1 minute. Rubber gloves should be worn to avoid exposure to hydrazine vapors.*

3. About 14 g. (17%) of hexafluoroacetone imine can be recovered during the redistillation step if the receivers for both distillations are cooled to −10° or lower. The yield of the hydrazone is about 67% if the recovered imine is taken into account.

4. Since acetic acid does not interfere with this reaction, a grade of lead tetraacetate that has been stabilized with acetic acid may be used.

5. The submitters have obtained yields as high as 90% on runs two times this scale.

6. *Caution! Toxicity data on this material are not available; therefore, it should be assumed to be as toxic as other diazo compounds and handled only in an efficient hood. Although it has been stored in stainless steel cylinders at autogenous pressure and handled without incident, contact with reagents likely to initiate rapid evolution of nitrogen should be carried out with caution.*

3. Discussion

Bis(trifluoromethyl)diazomethane has been prepared by the nitrosation of 1,1,1,3,3,3-hexafluoroisopropylamine[4] and by the present procedure,[5] which gives higher yields. Bis(perfluoroethyl)diazomethane has also been prepared by an extension of this method.[4]

Bis(trifluoromethyl)diazomethane is a reactive, electrophilic compound. It forms adducts with nucleophiles such as amines and phosphines[5] and adds to olefins, acetylenes,[5] and thiocarbonyl compounds[6] to form heterocycles. It has been used as a source of bis(trifluoromethyl) carbene in reactions with benzene,[5] saturated hydrocarbons,[7] carbon disulfide,[8] and transition metal compounds,[9] and it undergoes a unique radical chain reaction with saturated hydrocarbons to form adducts that are hydrazones and azines.[7]

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t-BUTYL AZIDOFORMATE

(Formic acid, azido, *t*-butyl ester)

$$(CH_3)_3COK + CO_2 \rightarrow (CH_3)_3COCO_2K$$

$$(CH_3)_3COCO_2K + ClP(O)(OC_2H_5)_2 \rightarrow (CH_3)_3COCO_2P(O)(OC_2H_5)_2$$

$$(CH_3)_3COCO_2P(O)(OC_2H_5)_2 + KN_3 \rightarrow (CH_3)_3COCON_3 + (C_2H_5O)_2PO_2K$$

Submitted by Michael A. Insalaco and D. Stanley Tarbell[1]
Checked by Frederick J. Sauter, Walter J. Campbell,
and Herbert O. House

1. Procedure

A. *t-Butylcarbonic diethylphosphoric anhydride.* A 500-ml. three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas inlet tube is dried in an oven and then flushed with nitrogen and allowed to cool while an atmosphere of nitrogen is maintained in the reaction vessel. To the flask are added successively 250 ml. of anhydrous tetrahydrofuran (Note 1) and 13.9 g. (0.12 mole) of alcohol-free potassium *t*-butoxide (Note 2). After the mixture has been stirred for 10 min under a nitrogen atmosphere to complete dissolution of the salt, the solution is cooled in an ice bath and then a slow stream of anhydrous carbon dioxide (Note 3) is bubbled through the cold solution for 1.5 hours with continuous stirring. While cooling, stirring, and the flow of carbon dioxide are maintained, a solution of 20.6 g. (0.12 mole) of pure diethyl phosphorochloridate (Note 4) in 50 ml. of anhydrous tetrahydrofuran (Note 1) is added dropwise to the reaction mixture and the cold reaction mixture is stirred for an additional 30 minutes under a carbon dioxide atmosphere. After the solvent has been removed from the reaction mixture by concentration at room temperature under reduced pressure with a rotary evaporator, the residual mixture of anhydride and potassium chloride is diluted with 300 ml. of anhydrous ether and then centrifuged to separate the insoluble salt. The residual salt is successively suspended in two 150-ml. portions of anhydrous ether and centrifuged to remove any remaining ether soluble product. After the combined ether solutions have been concentrated at reduced pressure and room temperature with a rotary evaporator, the crude anhydride remains as 25–28 g. (84–91%) of a colorless to pale yellow liquid (Note 5) which is sufficiently pure to be used for the preparation of *t*-butyl azidoformate.

B. *t-Butyl azidoformate.* A 300-ml. three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, and a gas inlet tube is dried in an oven and then flushed with nitrogen and allowed to cool while a nitrogen atmosphere is maintained in the reaction vessel. To the flask are added 120 ml. of anhydrous dimethyl sulfoxide (Note 6) and 8.1 g (0.10 mole) of powdered potassium azide (Note 7). While a nitrogen atmosphere is maintained in the reaction vessel, the mixture is stirred for 30 minutes to dissolve the bulk of the potassium azide, and then 25.4 g. (0.10 mole) of *t*-butylcarbonic diethylphosphoric anhydride is added dropwise with stirring. During this addition the temperature of the reaction mixture is maintained at approximately 25° by means of a water bath. The resulting solution is stirred at 20–25° for 1 hour and then 120 ml. of water is added dropwise while stirring and external cooling are maintained. The resulting mixture is extracted with three 120-ml. portions of pentane and the combined pentane extracts are washed successively with 20 ml. of water and 20 ml. of saturated aqueous sodium chloride solution. After the pentane solution has been dried over magnesium sulfate, the pentane is removed at room temperature under reduced pressure with a rotary evaporator. The residual crude product, 11–14 g. of a pale yellow liquid, is distilled under reduced pressure from a distilling flask heated in a water bath. *Caution! This distillation should be conducted in a hood behind a safety shield.* (Note 8). The product is collected as 7.2–9.3 g. (50–65%) of colorless liquid, b.p. 57–61° (40 mm.), n^{24}D 1.4224–1.4230 (Note 9).

2. Notes

1. A reagent grade of tetrahydrofuran should be redistilled from lithium aluminum hydride immediately before use. In this distillation discontinue heating when the residue in the stillpot has reached a volume of 50–100 ml.

2. Alcohol-free potassium *t*-butoxide, obtained from the MSA Research Corporation, Callery, Pennsylvania, should be weighed and transferred under anhydrous conditions.

3. The carbon dioxide, obtained from a cylinder or from a container packed with dry ice, should be passed through a drying tube packed with silica gel or anhydrous calcium sulfate.

4. The diethyl phosphorochloridate which is available from Stauffer Chemical Company, New York, should be redistilled before use: b.p. 60° (2 m.m.), n^{25}D 1.4153.

5. The anhydride has the following spectral characteristics: infrared (CCl_4), 1770 (C=O), 1255 and 1292 cm^{-1} (P=O); n.m.r. (CCl_4), δ 1.53 [9H singlet, $(CH_3)_3C$], 1.38 (6H pair of triplets, $J_{H\text{-}H} = 6.6$ Hz., $J_{P\text{-}H} = 2.5$ Hz., CH_3), and 4.17 (4H pair of quadruplets, $J_{H\text{-}H} = 6.6$ Hz., $J_{P\text{-}H} = 8.5$ Hz., CH_2).

6. An analytical grade of dimethyl sulfoxide obtained from J. T. Baker Co. or Matheson, Coleman and Bell was used. The checkers redistilled this solvent from calcium hydride before use; b.p. 83–85° (17 mm.).

7. A commercial grade of potassium azide, obtained from either Eastman Organic Chemicals or Alfa Inorganics, Inc., was purified by recrystallization from aqueous ethanol (1:2v/v) as previously described.[2] The pure azide, obtained as white solid, m.p. 343°, dec., was dried in an oven at 110° for 2 hours

before use. In this preparation it is preferable to use the more soluble potassium azide rather than sodium azide.

8. Although this distillation has been conducted repeatedly without incident, azides are potentially explosive.[3] Consequently, the distillation should be conducted behind a safety shield and the operator should wear protective equipment. The distilling flask should be heated by means of a water bath to avoid the possibility of overheating the distillation residue.

9. The product has the following spectral characteristics: infrared (CCl_4), 2170, 2120 (azide), 1760, and 1735 cm.$^{-1}$ (C=O); n.m.r. (CCl_4) δ 1.51 singlet, $(CH_3)_3C$; mass spectrum, m/e (rel. int.), 115 (17), 100 (16), 59 (85), 57 (20), 56 (41), 44 (18), 43 (84), 41 (21), 39 (19), 29 (30), 28 (100), 27 (21).

3. Discussion

t-Butyl azidoformate, a useful protective group for primary and secondary amino groups,[4–6] has been prepared previously from *t*-butyl carbazate.[3] The present procedure[7] is a more convenient preparative method. The intermediate carbonic phosphoric anhydride reacts with nucleophiles other than the azide ion in this preparation. Reaction of this anhydride with amines yields the *t*-butoxycarbonyl derivatives of amines.[7] Other carbonic phosphoric anhydrides have been prepared by procedures analogous to the method described here.[8]

1. Department of Chemistry, University of Rochester, Rochester, New York.
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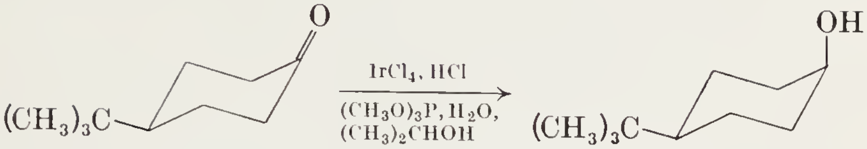
cis-4-*t*-BUTYLCYCLOHEXANOL

(Cyclohexanol, 4-*t*-butyl, *cis*)



Submitted by E. L. Eliel[1], T. W. Doyle, R. O. Hutchins,
and E. C. Gilbert
Checked by Mitchell Winnik and Ronald Breslow

1. Procedure

To a solution of 4.0 g. (0.012 mole) of iridium tetrachloride (Note 1) in 4.5 ml. of concentrated hydrochloric acid is added 180 ml. of water followed by 50 ml. of trimethyl phosphite (Note 2). This solution is added to a solution of 30.8 g. (0.20 mole) of 4-*t*-butylcyclohexanone (Note 3) in 635 ml. of 2-propanol contained in a 2-l. flask equipped with a reflux condenser. The solution is heated at reflux for 48 hours (Note 4). At the end of this time the 2-propanol is removed on a rotary evaporator at reduced pressure, and the remaining solution is diluted with 250 ml. of water and extracted with four 150-ml. portions of ether. The ether solution is washed with two 100-ml. portions of water which are combined with the aqueous residue (Note 5). The ether extract is dried over magnesium sulfate or potassium carbonate and then concentrated on a rotary evaporator at reduced pressure to obtain *cis*-4-*t*-butylcyclohexanol as a white solid (29–31 g.; 93–99%). Analysis of the crude product by glpc demonstrates it to contain 95.8–96.2 % *cis*-alcohol and 4.2–3.8 % of the *trans* isomer with essentially no ketone remaining (Note 6). Recrystallization from 40% aqueous ethanol affords greater than 99% pure *cis*-alcohol, m.p. 82–83.5° after sublimation[2] (Note 7).

2. Notes

1. Iridium tetrachloride was obtained from Platinium Chemicals, Inc., Box 565, Asbury Park, N.J. 07712 or from Alfa Inorganics, Inc., Box 159, Beverly, Mass. 01915.

2. The order of mixing the catalyst components is important for good results, and the sequence described should be followed. Particular care should be taken *not* to add the trimethyl phosphite before the water, as the reaction between it and concentrated hydrochloric acid is extremely violent.

3. 4-*t*-Butylcyclohexanone was obtained from Dow Chemical Company or Aldrich Chemical Co. Inc.

4. The reaction solution is often dark-colored at the beginning but lightens as reflux continues. The reflux time may be varied with the amount of ketone to be reduced. The completeness of the reaction may be followed by removing small aliquots, working up these samples as described in the text, and analyzing the product mixture by gas-liquid chromatography (see Note 6).

5. The iridium catalyst used in this preparation may be regenerated by reducing the volume of the aqueous residue to about 200 ml. at diminished pressure. This solution is then used instead of the iridium tetrachloride and water called for in the procedure.

6. The product was analyzed by gas-liquid chromatography using a 9-ft. 20% Carbowax 20M on 45/60 Chromosorb W column at 150°. The order of increasing retention times is: ketone, *cis*-alcohol, *trans*-alcohol.

7. Recrystallization is best accomplished by dissolving the crude product in hot ethanol (approx. 35 ml. per 10 g.) followed by adding water (approx. 25 ml. per 10 g.) and allowing the solution to cool slowly to 0°. The fluffy white needles are filtered using a sintered-glass funnel and dried over P_2O_5 at atmospheric pressure. Recooling the filtrate affords a second crop of product. Yield is 75–87%.

3. Discussion

4-*t*-Butylcyclohexanol has been prepared from *p*-*t*-butylphenol by reduction under a variety of conditions.[3,4] Eliel and Ro[2] obtained *cis*-rich 4-*t*-butylcyclohexanol by the reduction of 4-*t*-butylcyclohexanone with hydrogen on platinum oxide in glacial acetic acid containing some hydrogen chloride. Eliel and Nasipuri[5] have also obtained 4-*t*-butylcyclohexanol containing

80–92% of the *cis* isomer by the reduction of 4-*t*-butylcyclohexanone with isobornyloxyaluminum dichloride.

The present[6] procedure employs a readily available starting material and produces essentially pure *cis* isomer in good yield with little purification necessary. In view of the fact that the catalyst may be reused several times with little loss in stereoselectivity, the expense of the iridium tetrachloride is not a serious impediment.

The method is useful in the preparation of other axial alcohols. Henbest[6] has reported the reductions of 3-*t*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and cholestanone to the axial alcohols by this procedure, although for the preparation of 3-α-cholestanol the procedure of Edward[7] is preferred by the checkers. Recently[8] 2,4,4-trimethylcyclohexanone has been reduced to the pure axial alcohol by this method in 90% yield.

1. Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556.
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m-CHLOROPERBENZOIC ACID

(Peroxybenzoic acid, *m*-chloro-)

$$m\text{-}ClC_6H_4COCl + H_2O_2 + NaOH \xrightarrow[\text{dioxane}]{\substack{MgSO_4 \\ H_2O}} \xrightarrow{H_2SO_4} m\text{-}ClC_6H_4CO_3H$$

Submitted by Richard N. McDonald,[1] Richard N. Steppel, and James E Dorsey
Checked by William N. Washburn and Ronald Breslow

1. Procedure

In a 1-l. beaker (Note 1) equipped with a magnetic stirrer are placed 1.5 g. of magnesium sulfate heptahydrate, 36 g. of sodium hydroxide, 360 ml. of water, 90 ml. of 30% hydrogen peroxide, and 450 ml. of dioxane. This mixture is cooled to 15° by using an ice-water bath and by the addition of a small amount of ice to the mixture. *m*-Chlorobenzoyl chloride (52.5 g., 0.3 mole) (Note 2) is added in one portion while vigorous stirring is maintained. Small portions of ice are added to maintain the temperature below 25°. The reaction mixture is stirred at this temperature for 15 minutes and then transferred to a 3-l. separatory funnel. Cold 20% sulfuric acid (900 ml.) (Note 3) is added to the reaction mixture in the separatory funnel, and the mixture is shaken and separated. The aqueous layer is subsequently extracted with four 200-cc. portions of cold methylene chloride (Note 4). The combined extracts are dried over anhydrous magnesium sulfate and the methylene chloride removed under reduced pressure *via* a short path distillation (Note 5). After most of the solvent has been removed, a white pasty solid remains and the residual solvent is removed under full vacuum for an additional 2 hours or until a white, flaky powder remains. The product weighs approximately 51 g. Sodium thiosulfate analysis indicates 80–85% active oxygen present (Note 6).

2. Notes

1. The checkers used a Pyrex vessel; the submitters utilized a Nalgene beaker, because contact with the glass surface may catalyze the decomposition of the peracid.

2. The *m*-chlorobenzoyl chloride is prepared by refluxing *m*-chlorobenzoic acid, either commercial or recovered, with excess thionyl chloride. Distillation gives the *m*-chlorobenzoyl chloride in high yield, b.p. 112° (11 mm.).[2]

The recovery of the *m*-chlorobenzoic acid, the by-product from *m*-chloroperbenzoic acid oxidations, is facilitated by using methylene chloride as the solvent in peroxidations since the peracid is very soluble whereas the acid is quite insoluble.

3. The cold 20% sulfuric acid solution is made by adding the concentrated sulfuric acid (180 ml.) to crushed ice followed by the addition of more ice until the required volume is reached, *i.e.* 900 ml. The acid solution is then kept cold in an ice bath

until required. The methylene chloride is also precooled before use.

4. Iodometric titration of the moist extracts indicates approximately 51 g. of *m*-chloroperbenzoic acid present. A 4.0-ml. aliquot of the solution requires approximately 20 ml. of a 0.1000 *N* solution of sodium thiosulfate. To prepare the sample, 10 ml. of 10% sodium iodide and 5 ml. of acetic acid are added to the 5-ml. aliquot, and the mixture is diluted to 50 ml. The dark red solution is titrated to a pale yellow. At this point 1 ml. of starch solution is added and the titration continued to the end point, *i.e.*, a change from dark blue to clear.

$$\text{Total weight of peracid} = \frac{N_{Na_2S_2O_3} \cdot V_{Na_2S_2O_3(\text{ml.})} \cdot V_{\text{total extract (l.)}} \cdot 86.29}{V_{\text{aliquot (ml.)}}}$$

5. The methylene chloride solvent should be removed as rapidly as possible because contact with glass and heat cause decomposition of the peracid. A convenient method for the removal of the solvent involves a short-path vacuum distillation using a 2-l. distillation flask and trapping the solvent at dry ice or liquid nitrogen temperatures. The pressure should be reduced slowly at first and at least three traps used to minimize the amount of solvent introduced into the vacuum pump. Adjustment of a stopcock located between the first and second traps will help to control this problem. The distillation flask is placed in a water bath maintained between 25° and 35° so that the rate of solvent evaporation is quite rapid. Removal of the solvent over prolonged periods and drying of the solid peracid by excessive heating results in drastic losses of active oxygen. *m*-Chloroperbenzoic, once isolated, is stable over long periods of time when stored in polyethylene containers and refrigerated.

6. Iodometric titration of the solid product involves the use of 0.2-g. samples of the peracid and the procedure in Note 4.

$$\text{Per cent peracid} = \frac{N_{Na_2S_2O_3} \cdot V_{Na_2S_2O_3} \cdot 0.8629}{\text{Weight of sample}}$$

3. Discussion

This method is an extension of the reported perhydrolysis of certain other acid chlorides and anhydrides.[3] Although *m*-chloroperbenzoic acid is commercially available, this preparation requires only a short reaction time and simple equipment, and it affords high yields of this relatively stable and useful peracid. The methylene chloride-dioxane extracts can be stored and used directly for many peroxidations, in which case the total preparation time should not exceed 2 hours.

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1. Department of Chemistry, Kansas State University, Manhattan, Kansas 66502.
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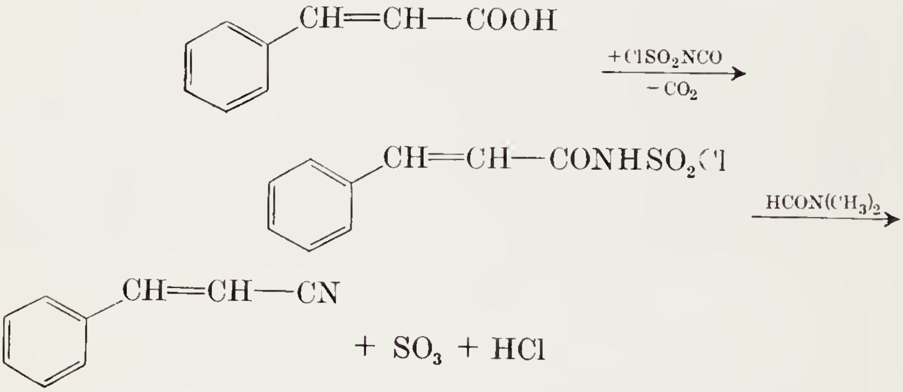
CINNAMONITRILE



Submitted by G. Lohaus[1]
Checked by Frank J. Weigert and Richard E. Benson

1. Procedure

Care! Chlorosulfonyl isocyanate is a highly corrosive, irritating compound. This reaction should be carried out in an efficient hood.

To a 2-l. four-necked flask equipped with a stirrer, thermometer, dropping funnel, and reflux condenser are added 296 g. (2 moles) of cinnamic acid and 600 ml. of methylene chloride. The mixture is heated to reflux and a solution of 290 g. (2.05 moles) of chlorosulfonyl isocyanate (Note 1) in 100 ml. of methylene chloride is added dropwise with stirring over a period of 45 minutes. After a few minutes the solution becomes clear and, after about one-half of the isocyanate has been added, the carboxylic acid amide N-sulfonyl chloride begins to precipitate. At the end of the addition, the reaction mixture is heated for an hour to complete the evolution of carbon dioxide (Note 2). Dimethylformamide (300 g., 4.1 moles) (Note 3) is added with stirring over a 15-minute period while cooling with ice to an internal temperature of 15–20°. The reaction mixture is stirred for an additional 15 minutes and then poured onto *ca.* 800 g. of ice. After the ice has melted, the resulting layers are separated and the aqueous phase is extracted once with 100 ml. of methylene chloride. The methylene chloride solutions are combined and extracted six times with 100-ml. portions of water to remove most of the dimethyl formamide (Note 4). The resulting organic solution is dried for 2 hours with 50 g. of potassium carbonate, the solution is decanted from the drying agent, and the methylene chloride is removed by distillation at atmospheric pressure. The resulting oil is distilled through a 10-cm. Vigreux column (Note 5) to give 197–225 g. (78–87%) of cinnamonitrile, b.p. 92–94° (1 mm.), $n^{25}D$1.5998 (Note 6). Its n.m.r. spectrum (60 MHz., carbon tetrachloride, 36°) shows two one-proton doublets at δ5.79 and 7.29 p.p.m. (J = 17 Hz.) and a five-proton singlet at δ7.35 p.p.m.

2. Notes

1. *Org. Syntheses*, **46,** 23 (1966). Chlorosulfonyl isocyanate is available from Farbwerke Hoechst AG. The checkers found it necessary to distill the product before use.

2. The rate of evolution of carbon dioxide can be followed easily with a bubble counter attached to the reflux condenser.

3. Other amides also can be used, but dimethylformamide generally is preferred because of its volatility, high solvent power, and miscibility with water.

4. The checkers found that, if the mixture at this point was allowed to stand overnight, a crystalline product separated that was identified as the dimethylformamide · sulfur trioxide complex.

5. The presence of a crystalline residue at the end of the distillation prevents the use of a spinning band column.

6. Gas chromatography indicates the purity to be greater than 99.9%. A column containing Chromosorb W/DMCS/AW with 10% Triton X 305 as the stationary phase is used.

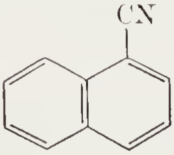
3. Discussion

This reaction illustrates a broadly applicable method for converting carboxylic acids to the corresponding nitriles.[2] It avoids the necessity for conversion of the acid to the amide to be followed by dehydration with the vigorous reagents phosphorus pentachloride or phosphorus oxychloride. The reaction is characterized by easy workup and generally good yields, and by mild reaction conditions that permit certain functional groups that may be present to remain unchanged. For example, the half ethyl ester of succinic acid is converted to the corresponding nitrile in 72% yield by this procedure. Aliphatic unsaturation may be present; thus 2,4-hexadienenitrile is obtained from 2,4-hexadienoic acid in 76% yield. The reaction is operable with chlorine-containing acids, and an aromatic acid has been converted to the nitrile by this procedure. The results are summarized in Table I.[2]

Other specific procedures for the synthesis of cinnamonitrile include the dehydration of cinnamamide with phosphorus

TABLE I

Nitriles Derived from Corresponding Acid

Nitrile	Yield, %
$C_6H_{11}CN$	78
$ClCH_2CH_2CN$	66
$(CH_3)_3CCN$	68
$CH_3CH{=}CHCH{=}CHCN$	76
$C_6H_5CH_2CN$	84
$C_2H_5OCOCH_2CH_2CN$	72
$NC\text{-}(CH_2)_8CN$	86
	63

pentachloride[3] or phosphorus oxychloride,[4] the dehydration of cinnamaldehyde oxime with acetic anhydride,[5] and the dehydrochlorination of α-chloro-β-phenylpropionitrile with quinoline,[6,7] N,N-diethylaniline,[8] or triethylamine.[9]

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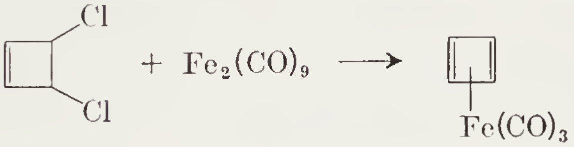
CYCLOBUTADIENEIRON TRICARBONYL

(1,3-Cyclobutadiene, iron tricarbonyl complex)



Submitted by R. Pettit[1] and J. Henery
Checked by J. Napierski and R. Breslow

1. Procedure

In a well-ventilated hood a 500-ml. three-necked flask is immersed in an oil bath and fitted with a condenser and a mechanical stirrer; a T-piece is inserted through a rubber stopper placed in the top of the condenser, one lead of the T-piece being connected to a nitrogen supply and the other to a gas bubbler. *cis*-3,4-Dichlorocyclobutene[2], 20 g. (0.163 mole), and 125 ml. of anhydrous benzene are added to the flask and the apparatus is flushed with nitrogen. Diiron enneacarbonyl, 25 g. (Note 1) is then added, the flow of N_2 is stopped, and the mixture is heated to 50–55° with stirring. After about 15 minutes the initial rapid evolution of carbon monoxide becomes greatly diminished and a further 8 g. of $Fe_2(CO)_9$ is added. Additional 8-g. quantities of $Fe_2(CO)_9$ are added at intervals (approximately 15 minutes) governed by the rate of carbon monoxide evolution. The addition is continued until no more carbon monoxide is liberated (Note 2) and the reaction mixture stirred at 50° for an additional hour. Approximately 140 g. of $Fe_2(CO)_9$ is required for the complete conversion of the dichlorocyclobutene, the total reaction time being about 6 hours.

The contents of the flask are then filtered with suction through Filtercel and the residue, while kept in the Buchner funnel, is thoroughly washed with pentane until the washings are colorless (Note 3). The pentane and much of the benzene are evaporated from the combined filtrates by means of a water aspirator.

The residual liquid is then transferred to a flask equipped with a fairly efficient fractionating column and distilled under reduced pressure. Benzene is removed first followed by considerable quantities of iron pentacarbonyl (b.p. 20°, 30 mm.); when the $Fe(CO)_5$ has been removed, the pressure is reduced further and cyclobutadieneiron tricarbonyl[4] is collected as a pale yellow oil, b.p. 47° (3 mm.). Yield 13.8–14.4 g. (45–46% based on dichlorocyclobutene) (Note 4).

2. Notes

1. $Fe_2(CO)_9$ is readily available through photolysis of iron pentacarbonyl.[3]

2. The conversion of the dichlorocyclobutene to cyclobutadieneiron tricarbonyl can be conveniently monitored by vapor phase chromatography. On a 5 ft. × $\frac{1}{8}$ in. column of 20% Carbowax on Chromosorb W, under conditions where the retention time of dichlorocyclobutene is 2.6 minutes, the retention time of cyclobutadieneiron tricarbonyl is 2.4 minutes.

3. The brown insoluble residue is frequently pyrophoric if it is allowed to dry; it should be immediately wetted with water before it is disposed of.

4. In some preparations the last portion of the distillate of the complex may be dark green in color. This color is due to trace

amounts of $Fe_3(CO)_{12}$. If desired, this can be readily removed by chromatography over alumina. The submitters report a similar yield on three times the scale.

3. Discussion

Cyclobutadieneiron tricarbonyl may also be produced through reaction of 3,4-dichlorocyclobutene with $Na_2Fe(CO)_4$,[5] and by irradiation of α-pyrone followed by treatment with $Fe_2(CO)_9$[6]. The method outlined here is the most convenient procedure especially when considerable quantities (10 g. or more) of cyclobutadieneiron tricarbonyl are required. The analogous reaction of derivatives of 3,4-dihalocyclobutenes with $Fe_2(CO)_9$ affords the corresponding cyclobutadieneiron tricarbonyl complexes. Cyclobutadieneiron tricarbonyl can be oxidized to generate cyclobutadiene *in situ*.[7]

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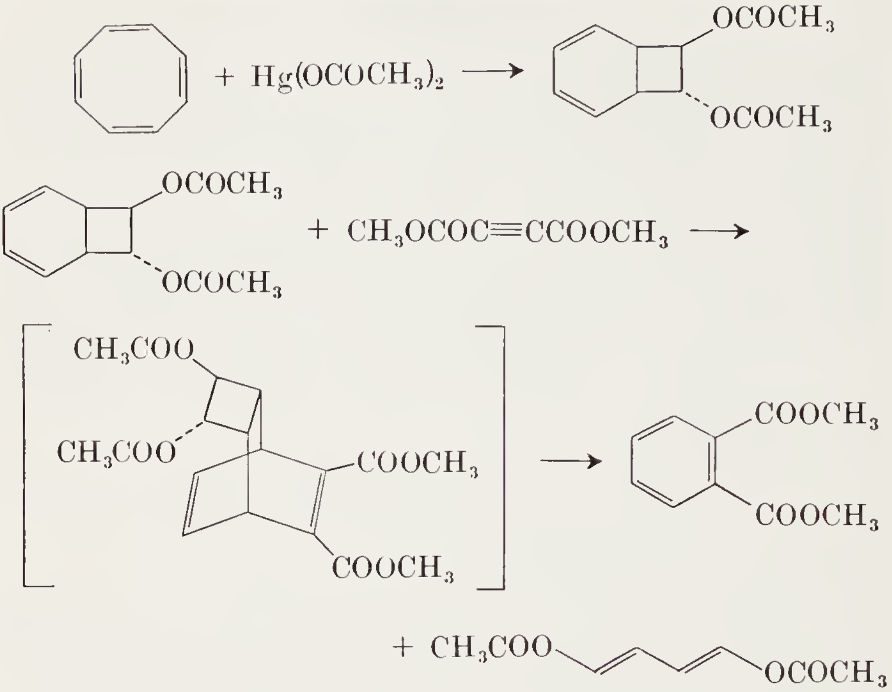
trans,trans-1,4-DIACETOXY-1,3-BUTADIENE

(1,3-Butadiene-1,4-diol, *trans,trans*-, diacetate)



Submitted by Robert M. Carlson and Richard K. Hill[1]
Checked by Jack M. Pal and Peter Yates

1. Procedure

A. *trans-7,8-Diacetoxybicyclo*[4.2.0]*octa-2,4-diene.* In a 1-l. three-necked flask fitted with a reflux condenser, an efficient stirrer, and a thermometer dipping well into the solution is placed a suspension of mercuric acetate (Note 1) (160 g., 0.50 mole) in glacial acetic acid (400 ml). While the suspension is stirred, cyclooctatetraene (52.0 g., 0.50 mole) (Note 2) is added rapidly. The white addition compound that separates after 10–15 minutes is decomposed by careful heating of the reaction mixture at 70–75° for 2 hours (Note 3). While still warm, the mixture is poured through funnels containing glass wool plugs into two 4-l. beakers, each containing 2 l. of water (Note 4). The mixture is allowed to stand for several hours, and the solid that separates is collected on a Buchner funnel and pressed as dry as possible on the funnel. The moist, yellow solid is spread out on a large piece of filter paper and allowed to dry overnight. The yield of *trans*-7,8-diacetoxybicyclo[4.2.0]octa-2,4-diene, m.p. 52–55°, is 83–86 g. (75–77.5%) (Note 5); it may be used in the next step without further purification (Note 6).

B. *trans, trans*-1,4-*Diacetoxy*-1,3-*butadiene.* The diacetate above (83.0 g., 0.373 mole), dimethyl acetylenedicarboxylate[2] (54.0 g., 0.380 mole), and benzene (250 ml.) are placed in a 500-ml. flask and boiled under reflux for 6 hours (Note 7). The solution is filtered to remove the remaining mercury and mercuric salts, and the benzene is distilled under reduced pressure. The residual viscous yellow oil is distilled under reduced pressure (Note 8). A mixture of 1,4-diacetoxy-1,3-butadiene and dimethyl phthalate is collected at 140–155° (18–20 mm.), bath temperature 170–200°, from which the diene crystallizes as colorless needles in the cooled receiver. The solid in the receiver is broken up and washed onto a Buchner funnel with petroleum ether (b.p. 60–70°). The solid is then pressed between sheets of filter paper to remove excess dimethyl phthalate and recrystallized from acetone-petroleum ether (b.p. 60–70°) (*ca.* 1:2) (Note 9). The yield of colorless needles of *trans,trans*-1,4-diacetoxy-1,3-butadiene, m.p. 102–104°, is 26–31 g. (41–49%) (Notes 10, 11, and 12).

2. Notes

1. "Baker analyzed" mercuric acetate was used as obtained from J. T. Baker Chemical Company.

2. Cyclooctatetraene was used as obtained from Badische Anilin- und Soda-Fabrik, 67 Ludwigshafen, Rhein, Germany.

3. Temperatures in excess of 75° cause darkening of the reaction mixture. The submitters found that adequate temperature control could be maintained with a Bunsen flame; the checkers used a heating mantle.

4. This operation should be carried out in a well-ventilated hood. Scratching the sides of the beakers at the surface of the water promotes crystallization. The beakers are stirred

occasionally to promote rapid crystallization and to minimize the formation of a solid cake on the bottom.

5. The checkers obtained 92–93 g. (83–84%); m.p. 58–61°.

6. Melting points of 61–62°, 61.4–62.5°, 64–65°, and 66° have been reported[3-5] The diacetate may be recrystallized from aqueous acetic acid,[3-5] ligroin,[3] or ethanol.[4]

7. A longer reflux period, *e.g.*, overnight, did not affect the yield.

8. The submitters used a 500-ml. distilling flask with a 250-ml. distilling flask as receiver. The side arm of the distilling flask was extended, if necessary, by means of a Tygon joint into the bulb of the receiver. The receiver was cooled by a stream of cold water. The distillation was continued until about three-fourths of the material in the flask had distilled. The checkers used standard-taper glassware for the distillation; they found it necessary to heat the distillation adapter with a microburner from time to time in order to prevent plugging by solidified product. They continued the distillation until no further solid product distilled.

9. The checkers found that it was essential to conduct the recrystallization rapidly in order to obtain maximum yields.

10. The checkers obtained a yield of 40.8 g. (64%) when distillation of the product mixture was continued until no further solid product distilled (cf. Notes 8 and 9).

11. A satisfactory alternative to recrystallization of the diene is the following. The crude solid is placed in a 100-ml. beaker containing 40–50 ml. of a 15% solution of acetone in petroleum ether (b.p. 60–70°). The lumps are broken up, and the colorless solid is filtered from the pale yellow solution. A final wash with 20 ml. of ice-cold acetone leaves 31–32 g. of diene, m.p. 99–102°, pure enough for many purposes.

12. The infrared and ultraviolet spectra of the product have been reported.[6]

3. Discussion

This method is essentially that described by Reppe, Schlichting, Klager, and Toepel,[3] although the correct structures were assigned by others.[4,7] 7,8-Diacetoxybicyclo[4.2.0]octa-2,4-diene has also been prepared by oxidation of cyclooctatetraene with lead tetraacetate,[5] and by chlorination of cyclooctatetraene with sulfuryl chloride followed by displacement with potassium acetate.[3,7] The two other geometric isomers of the diene have been prepared by another method.[6] *trans,trans*, 1,4-Diacetoxy-1,3-butadiene is a reactive diene in the Diels-Alder reaction. It has been used as the starting material in stereospecific syntheses of conduritol-D[8] and shikimic acid,[9,10] and in a simple general method of preparation of benzene derivatives, especially unsymmetrical biphenyls.[11,12]

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2-DIAZOPROPANE

(Dimethyldiazomethane)

$$(CH_3)_2C{=}NNH_2 \xrightarrow[\text{KOH}]{\text{HgO}} (CH_3)_2CN_2$$

Submitted by S. D. Andrews,[1] A. C. Day,[1] P. Raymond,[1]
and M. C. Whiting[2]
Checked by G. Swift and W. D. Emmons

1. Procedure

Caution! 2-Diazopropane is volatile and presumably toxic. All operations should be carried out in an efficient hood behind a protective screen.

A 250-ml. two-necked round-bottomed flask is arranged for magnetic stirring in a bath of water at room temperature (*ca.* 20°). The flask is equipped with a dropping funnel and distillation head carrying a thermometer, and is connected *via* an acetone-dry ice condenser to a receiver which is cooled to −78° in acetone and dry ice. In the distilling flask are placed 60 g. (0.27 mole) of yellow mercuric oxide (Note 1), 100 ml. of ether (Note 2), and 4.5 ml. of a 3 *M* solution of potassium hydroxide in ethanol (Note 3). The pressure throughout the system is reduced to 250 mm., and with vigorous stirring 15 g. (0.21 mole) of acetone hydrazone (Note 4) is added dropwise through the funnel (Note 5). With continued stirring, the pressure is reduced to 15 mm., and ether and 2-diazopropane codistill and condense in the receiver (Note 6). The yield of product is 70–90% (Notes 7, 8, and 9).

2. Notes

1. British Drug Houses' Laboratory Reagent yellow mercuric oxide was used for most runs. The preparation was not apparently improved by the use of freshly precipitated mercuric oxide.

2. The quantity of ether can be varied over a wide range (the submitters have successfully used as little as 60 ml.), and is adjusted to yield the desired concentration of 2-diazopropane in the distillate.

3. A stock solution of potassium hydroxide in ethanol was prepared and stored under nitrogen. Old stocks are brown and contain a dark sediment, but they are apparently just as effective as the freshly prepared reagent. Methanolic potassium hydroxide has also been used by the submitters; this remains clear and colorless for long periods but offers no other advantage over the ethanolic solution. In absence of the basic solution, the acetone hydrazone is not oxidized by mercuric oxide.

4. This volume, p. 3. Yields are lower if the hydrazone is not freshly redistilled.

5. No special precautions are necessary to keep the reaction mixture cool, since boiling of the ether provides adequate cooling.

6. It is usually unnecessary to dry the distillate, because the water produced in the reaction is largely retained in the distilling flask. That which vaporizes is trapped as ice in the condenser.

7. The solution is *ca.* 2 *M*. Yields were determined by nitrogen evolution on adding acetic acid, or spectrometrically from the visible absorption band at 500 mμ, which has $\varepsilon \sim 2$ as calculated from the nitrogen evolution. Yields estimated by addition of a standard solution of benzoic acid and titration with alkali were consistently much lower. Both methods underestimate the yield, since decomposition with acid gives tetramethylethylene and some acetone azine in addition to the isopropyl ester.[3] The nitrogen evolution method (and therefore the spectrometric method) probably underestimates the yield by *ca.* 10–20%, the titration method by more than 50%.

8. The entire preparation is very rapid (*ca.* 30 minutes) and is easily adaptable for the preparation of larger amounts of 2-diazopropane. Without difficulty, 2–3 *M* solutions can be obtained (see Note 2). The solutions are essentially mercury-free.

9. 2-Diazopropane is an unstable material. The decay is first-order with a half-life of 3 hours at 0°.

3. Discussion

This method[4] is an adaptation of that given by Staudinger and Gaule.[5] Highly unstable solutions have been obtained by Applequist and Babad[5] by use of silver oxide in place of mercuric oxide.

Contrary to previous reports,[5–7] 2-diazopropane as indicated by the present procedure is neither difficult to prepare nor unduly unstable. The method may be extended to other secondary aliphatic diazo compounds which have given difficulty in the past.[8] The success of the method depends on the use of a basic catalyst for the oxidation. The desirability of a basic catalyst has been recognized previously[9,10] and is well illustrated by the contrast between the two preparations of diphenyldiazomethane[16,11] (contrast also refs. 9 and 12). Miller has speculated on the role of the basic catalyst.[16]

2-Diazopropane is a potential source of *gem*-dimethyl groups. It undergoes 1,3-dipolar addition to acetylenes[13] and allenes,[14] and the adducts can be photolyzed to give cyclopropenes[15] or methylenecyclopropanes,[16] respectively. In certain cases the adducts from α-substituted acetylenes give good yields of allenes and conjugated dienes on photolysis.[13]

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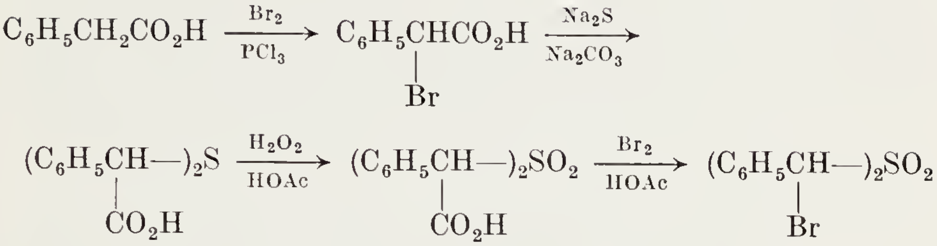
α,α′-DIBROMODIBENZYL SULFONE
(Sulfone, bis(α-bromobenzyl))

METHOD I



$$C_6H_5CH_2CO_2H \xrightarrow[PCl_3]{Br_2} \underset{\displaystyle Br}{\underset{|}{C_6H_5CHCO_2H}} \xrightarrow[Na_2CO_3]{Na_2S}$$

$$(\underset{\displaystyle CO_2H}{\underset{|}{C_6H_5CH}}—)_2S \xrightarrow[HOAc]{H_2O_2} (\underset{\displaystyle CO_2H}{\underset{|}{C_6H_5CH}}—)_2SO_2 \xrightarrow[HOAc]{Br_2} (\underset{\displaystyle Br}{\underset{|}{C_6H_5CH}}—)_2SO_2$$

Submitted by LOUIS A. CARPINO and LOUIS V. MCADAMS, III[1]
Checked by TIMOTHY P. HIGGS and RONALD BRESLOW

1. Procedure

A. *α-Bromophenylacetic acid.* In a 3-l. round-bottomed flask fitted with a mechanical stirrer and an efficient reflux condenser (Note 1) are placed 750 ml. of benzene, 230 g. (1.69 moles) of phenylacetic acid (Note 2), 15 g. of phosphorus trichloride and 288 g. (1.80 moles) of bromine (Note 3). The resulting solution is heated at gentle reflux for 2–3 days until the initial bromine color is discharged. The solution is allowed to cool to room temperature and after 1 hour is decanted from some polymeric material into a 2-l. distilling flask. Removal of the solvent by distillation from a water bath with the aid of a water aspirator gives a black oil which is poured into 250–300 ml. of ligroin (b.p. 90–120°). The mixture is heated to dissolve the oil and the solution is stored at −25° in a freezer for 12 hours. Filtration on a sintered-glass funnel followed by washing with 200 ml. of cold (10°) ligroin (b.p. 90–120°) gives 243 g. (67%) of the α-bromophenylacetic acid as a white solid, m.p. 73–83°. Recrystallization from about 400 ml. of ligroin (b.p. 90–120°) with 15 g. of decolorizing carbon affords 217–233 g. (60–62%) of the purified acid, m.p. 80.5–84°.

B. *α,α′-Diphenylthiodiglycolic acid.* In a 4-l. Erlenmeyer flask a suspension of 223 g. (1.04 moles) of α-bromophenylacetic acid in 1.25 l. of water is brought into solution by addition of a solution of 157 g. (1.48 moles) of sodium carbonate in 700 ml. of water. There is then added a solution of 104 g. (0.8 mole) of sodium sulfide (60–62% pure fused flakes) (Note 4) in 700 ml. of water. The resulting mixture is stirred mechanically at room temperature for 3 hours, heated to the boiling point, filtered while hot, cooled, and cautiously acidified (in a hood) with 3 *N* hydrochloric acid. Filtration followed by washing with 200 ml. of water yields 135–140 g. (86–89%) of crude acid, m.p. 130–140°. The crude material is sufficiently pure for use in the next step (Note 5).

C. *α,α′-Dibromodibenzyl sulfone.* To a solution of 24.9 g. (0.082 mole) of crude α,α′-diphenylthiodiglycolic acid in 250 ml. of glacial acetic acid contained in a 500-ml. three-necked round-bottomed flask fitted with a bulb condenser there is added over a 30-minute period, with ice bath cooling and stirring by means of a magnetic stirrer, 37.4 g. (0.33 mole) of 30% hydrogen peroxide. The mixture is allowed to come to room temperature (Note 6) and after 3 days there is added in one portion 30 g. (0.188 mole) of bromine and 30 g. of potassium bromide in 150 ml. of water. A sunlamp (Note 7), focused on the reaction mixture from a distance of 1 in., causes the solution to warm to 80° (Note 8). After heating at 80° for 30 minutes the mixture is cooled, the solid filtered and washed with water and ethanol to give 9–10 g. (27–30%) of crude α,α′-dibromodibenzyl sulfone, m.p. 135–150°. The crude mixture of diastereomers is pure enough to be used directly in the synthesis of 2,3-diphenylvinylene sulfone (Note 9).

2. Notes

1. An efficient bulb condenser (Allihn) was used to prevent loss of bromine.

2. The phenylacetic acid was used as supplied by the Eastman Kodak Co.

3. The bromine was washed just before use in a separatory funnel with 200 ml. of concentrated sulfuric acid.

4. The sodium sulfide was dissolved in the aqueous solution

by warming, but the solution was cooled to room temperature before addition. The checkers used 192 g. (0.8 mole) $Na_2S \cdot 9\ H_2O$.

5. After repeated crystallization from nitromethane the *meso* isomer, m.p. 177–180°, was obtained in a pure state in low yield.

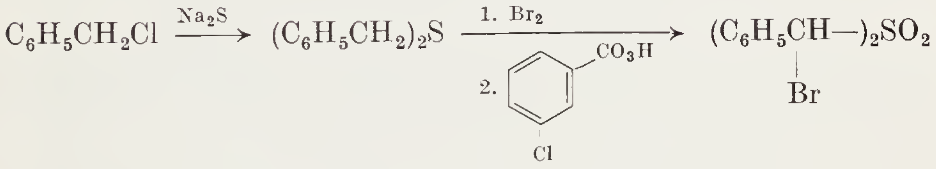
6. After a few hours a precipitate appeared but it generally redissolved after 1.5 days. If the precipitate had not dissolved, it could be brought into solution by heating. The solution was then cooled before addition of bromine.

7. A General Electric 275-watt sunlamp was used.

8. The heat of the sunlamp maintained the temperature near 80°. For larger runs a heating mantle must be used to keep the temperature near 80°.

9. By recrystallization from ethanol it was possible to separate two isomeric dibromides of m.p. 155–157.5° and 162–164° in low yield.

METHOD II



1. Procedure

A. *Dibenzyl sulfide.* A solution prepared from 25.8 g. (0.2 mole) of benzyl chloride and 75 ml. of 95% ethanol contained in a 250-ml. round-bottomed flask equipped with an efficient bulb condenser (Allihn) and a magnetic stirrer is brought to gentle reflux by means of a heating mantle. With stirring and heating there is added over a 4-hour period through a dropping funnel 36 g. (0.15 mole) of sodium sulfide nonahydrate dissolved in 50 ml. of water. The solution is heated at reflux for 3 days, after which the ethanol is removed by distillation at atmospheric pressure. The hot aqueous solution is poured with stirring into a 250-ml. beaker half-filled with chipped ice. After the ice has melted, the resulting yellow solid is filtered on a Buchner funnel and washed with 50 ml. of water. After air-drying the solid is distilled from an ordinary 50-ml. Claisen flask to give 17.6 g.

(80%) of dibenzyl sulfide, b.p. 120° (0.15 mm.) (Note 1). The sulfide is pure enough to use directly in the next step. Recrystallization from 70% ethanol gave a pure sample, m.p. 46–48°.

B. *α,α'-Dibromodibenzyl sulfone.* To a gently refluxing solution of 11.35 g. (0.053 mole) of dibenzyl sulfide in 150 ml. of carbon tetrachloride (Note 2) contained in a three-necked round-bottomed flask there is added dropwise over a period of 1.5 hours a solution prepared from 17.6 g. (0.11 mole) of bromine dissolved in 50 ml. of carbon tetrachloride while a sunlamp (Note 3) is focused on the reaction mixture from a distance of 1 in. The solution is refluxed by means of a heating mantle for 3 hours and the carbon tetrachloride removed from a water bath at 50° with the aid of a water aspirator. To the residual dark oil there is added 25 ml. of anhydrous ether (Note 4), and after cooling in an ice bath a solution of 32.5 (0.15 mole) of *m*-chloroperbenzoic acid (Note 5) in 150 ml. of anhydrous ether is added dropwise over a 30-minute period. The mixture is then allowed to warm to room temperature and stirred for 2 days.

The solvent is evaporated by means of an air jet at room temperature, and to the residual solid there is added saturated sodium bicarbonate solution until effervescence ceases. Filtration of the remaining solid followed by washing with water and cold ethanol gives 6.5 g. (30%) of crude α,α'-dibromodibenzyl sulfone, m.p. 142–158°. This mixture of diastereomers is pure enough for use in conversion to 2,3-diphenylvinylene sulfone (Note 6).

2. Notes

1. The submitters report a similar percent yield on twenty times the scale.
2. The carbon tetrachloride was freshly distilled over phosphorus pentoxide.
3. A General Electric 275-watt sunlamp was used.
4. The ether was dried over sodium metal.
5. The *m*-chloroperbenzoic acid (assay: 85%) was used either as supplied by FMC Corporation or prepared as described in this volume, p. 15.
6. Repeated fractional crystallization from ethanol gave in

low yield pure samples of the same two diastereomeric dibromides, m.p. 155–157.5° and 162–164°, obtained previously through application of Method I.

3. Discussion

α-Bromophenylacetic acid has been prepared by the bromination of phenylacetic acid by means of elemental bromine at high temperature[2] or under ultraviolet irradiation[3] or by means of N-bromosuccinimide,[4] and by treatment of mandelic acid with phosphorus and bromine[5] or fuming hydrobromic acid.[6] α,α′-Diphenylthiodiglycolic acid has been prepared by reaction of α-bromophenylacetic acid with sodium sulfide.[7] Benzyl sulfide has been obtained from benzyl chloride and potassium sulfide[8] or benzylmercaptide.[9] α,α′-Dibromodibenzyl sulfone has been obtained by oxidation and subsequent brominative decarboxylation of α,α′-diphenylthiodiglycolic acid[10] or by bromination and subsequent oxidation of benzyl sulfide.[10]

Both methods of preparation represent general techniques for the synthesis of α,α′-dibromodibenzyl sulfones which are key intermediates in the synthesis of the vinylene sulfones.

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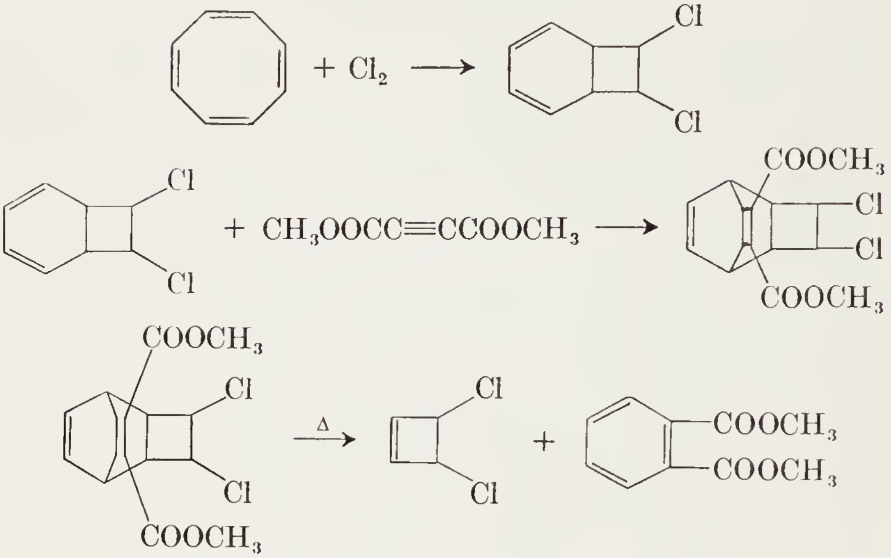
cis-3,4-DICHLOROCYCLOBUTENE

(Cyclobutene, 3,4-dichloro, *cis*-)



Submitted by R. Pettit and J. Henery[1]
Checked by J. Napierski and R. Breslow

1. Procedure

Dry chlorine gas is admitted into a solution of 104 g. (1.0 mole) of cyclooctatetraene and 150 ml. of dry carbon tetrachloride contained in a tared 500-ml. three-necked flask equipped with a gas inlet tube, a low-temperature thermometer, and a calcium chloride drying tube. The reaction mixture is maintained between −28° and −30° throughout the addition, which is then terminated after 71 g. (1.0 mole) of chlorine has been added. After the addition, which takes approximately 1 hour, the reaction mixture is allowed to warm to 0° and 50 g. of powdered sodium carbonate is added and the contents then shaken gently for several minutes. This treatment removes any HCl which may have been produced during the reaction. The mixture is then filtered directly into a 1-l. round-bottomed flask containing 135 g. (0.95 mole) of dimethyl acetylenedicarboxylate. A condenser is fitted to the flask and the solution is heated at gentle reflux for 3 hours (Note 1). The solvent is then removed under reduced pressure (Note 2). The crude Diels-Alder adduct, which will slowly solidify on standing, is used directly in the next step.

The crude Diels-Alder adduct is transferred to a 500-ml. pressure-equalizing dropping funnel which is attached to a 1-l. three-necked round-bottomed flask; the latter is immersed in an oil bath maintained at 200° and is equipped with a distillation head, condenser, and receiving flask. The pressure inside the equipment is reduced to 20 mm. A magnetic stirrer in the pyrolysis flask is started, the Diels-Alder adduct (Note 3) is then added slowly to the hot flask and the pyrolysate collected in the receiving flask. The distillation temperature during the pyrolysis varies from 135° to 152°, depending on the rate of addition of the Diels-Alder adduct. After the addition is complete (about 1 hour), the pyrolysis is continued for a further 30 minutes or until very little material remains in the pyrolysis flask (Note 4). The crude pyrolysate is then redistilled at 12–15 mm., all the material boiling below 140° being collected; this distillate consists mainly of a mixture of dichlorocyclobutene and 1,4-dichlorobutadiene, the residue being mainly dimethylphthalate.

A final distillation at 55 mm. through a 36-in. platinum spinning band column yields 49–52 g. (40–43%) of pure *cis*-3,4-dichlorocyclobutene (b.p. 70–71°, 55 mm.); the forerun (b.p. 58–62°, 55 mm.) consists mainly of 1,4-dichlorobutadiene (Note 5).

2. Notes

1. The reaction is very exothermic and usually it is necessary to remove the external source of heat for a short period as soon as reflux has started.

2. Slight warming and pressures of about 1 mm. are required to remove the last of the solvent.

3. A sun lamp situated close to the funnel may be required to prevent solidification of the Diels-Alder adduct.

4. It is necessary to keep the internal pressure close to 20 mm. (place a manometer in the line). If lower pressures are used, the Diels-Alder adduct itself will distill over; if higher pressures are

maintained, the rate of removal of the dichlorocyclobutene from the hot reaction flask is reduced and extensive thermal rearrangement to 1,4-dichlorobutadiene will occur.

5. A good fractionating column is required to separate the 1,4-dichlorobutadiene from the dichlorocyclobutene. At 55 mm. the dichlorobutadiene will distill at 58–62°; after this material has been removed, the temperature will rise fairly sharply to 70° and at this point the reflux ratio may then be reduced from 10:1 to zero and the dichlorocyclobutene collected quickly. It usually is necessary to apply heat frequently with a sun lamp to prevent solidification of the dichlorobutadiene in the exit tube of the distillation apparatus, especially if the receiving flask is kept cold.

3. Discussion

This method of preparation, which is due to Nenitzescu, Avram, Marica, Dinulescu, Farcasiu, Elian, and Mateescu,[2] is the only practical method available at this time for the preparation of 3,4-dichlorocyclobutene.

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1. Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712.
2. M. Avram, E. Marica, I. Dinulescu, M. Farcasiu, M. Elian, G. Mateescu, and C. D. Nenitzescu, *Chem. Ber.*, **97**, 372 (1964).

DIETHYL *t*-BUTYLMALONATE

(Malonic acid, *t*-butyl-, diethyl ester)

$$CH_2(CO_2C_2H_5)_2 + CH_3COCH_3 \xrightarrow[\substack{(CH_3CO)_2O,\\ \text{reflux}}]{ZnCl_2} (CH_3)_2C{=}C(CO_2C_2H_5)_2$$

$$(CH_3)_2C{=}C(CO_2C_2H_5)_2 + CH_3MgI \xrightarrow[(C_2H_5)_2O]{CuCl} \xrightarrow[H_2SO_4]{H_2O} (CH_3)_3CCH(CO_2C_2H_5)_2$$

Submitted by E. L. Eliel, R. O. Hutchins, and Sr. M. Knoeber[1]
Checked by Walter J. Campbell and Herbert O. House

1. Procedure

A. *Diethyl isopropylidenemalonate.* In a 2-l. flask equipped with a magnetic stirrer and a reflux condenser fitted with a calcium chloride drying tube are placed 400 g. (2.50 moles) of diethyl malonate (Note 1), 216 g. (3.73 moles) of acetone (Note 2), 320 g. (3.14 moles) of acetic anhydride, and 50 g. (0.37 mole) of anhydrous zinc chloride (assay 98.9%, Note 3). The solution is heated at reflux with stirring for 20–24 hours and then cooled and diluted with 300–350 ml. of benzene. The resulting dark-colored solution is washed with four 500-ml. portions of water and the combined aqueous layers are extracted with two 100-ml. portions of benzene. The combined benzene solutions are concentrated under reduced pressure with a rotary evaporator, and the residual liquid is fractionally distilled under reduced pressure through a 30-cm. Vigreux column or spinning band column. After separation of the unchanged diethyl malonate [119–135 g., b.p. 85–87° (9 mm.)] and intermediate fractions [b.p. 87–104° (9 mm.)], the diethyl isopropylidenemalonate is collected as 231–246 g. (46–49%) of colorless liquid, b.p. 110–115° (9–10 mm.), $n^{20}\text{D}$ 1.4483–1.4490 (Note 4).

B. *Diethyl t-butylmalonate.* A 1-l. three-necked flask fitted with a mechanical stirrer, a pressure-equalizing dropping funnel, a reflux condenser, and a nitrogen inlet tube is dried in an oven at 110–120° and then flushed with nitrogen and allowed to cool; an atmosphere of nitrogen is maintained in the reaction vessel throughout the subsequently described reactions. After 18.3 g. (0.75 g. atom) of magnesium turnings has been placed in the flask, a solution of 113.5 g. (0.80 mole) of methyl iodide (Note 5) in 200 ml. of anhydrous diethyl ether (Note 6) is added dropwise with stirring. The resulting solution of methylmagnesium iodide is cooled to 0–5° with an external ice-salt bath, and 1.0 g. (0.010 mole) of copper(I) chloride is introduced with stirring (Note 7). The temperature of the resulting mixture is kept at −5° to 0° while a solution of 100 g. (0.500 mole) of diethyl isopropylidenemalonate in 100 ml. of anhydrous diethyl ether (Note 6) is added, dropwise and with stirring over a period of 80–90 minutes. After the addition is complete, the cooling bath is removed and the reaction mixture is stirred for 30 minutes and then poured onto a mixture of 500–1000 g. of ice and 400 ml. of aqueous 10% sulfuric acid. The ether layer is separated and the aqueous phase is extracted with three 200-ml. portions of diethyl ether. The combined ether solutions are washed with 100 ml. of saturated aqueous sodium thiosulfate (Note 8) and then dried over magnesium sulfate and concentrated under reduced pressure with a rotary evaporator. The residual liquid is distilled through a short Vigreux column to separate 93.5–102 g. (87–94%) of the diethyl *t*-butylmalonate as a colorless liquid, b.p. 60–61° (0.7 mm.), $n^{20}\text{D}$ 1.4250 (Note 9).

2. Notes

1. A commercial grade of diethyl malonate was distilled before use, b.p. 90° (15 mm.).

2. The submitters used commercial acetone which was dried over potassium carbonate before use. The checkers dried the acetone over Linde Molecular Sieves, No. 4A.

3. The checkers used a proportionate amount (52 g.) of anhydrous zinc chloride (assay, 95% minimum) purchased from the Mallinckrodt Chemical Works.

4. This procedure was described by Cope and Hancock.[2] The product has infrared absorption (CCl_4 solution) at 1730 (conjugated ester C=O) and 1650 cm.$^{-1}$ (conjugated C=C) with n.m.r. peaks (CCl_4 solution) at δ 4.10 (4 H quadruplet, $J = 7$ Hz.), 2.01 (6 H singlet), and 1.12 (6 H triplet, $J = 7$ Hz.) and an ultraviolet maximum (95% EtOH solution) at 218 mμ (ε 10,200).

5. Reagent grade methyl iodide, obtained from J. T. Baker Chemical Company, Philadelphia, was used without further purification. The checkers used a pure grade of methyl iodide purchased from Eastman Organic Chemicals without further purification.

6. The solvent obtained from freshly opened containers of anhydrous diethyl ether, obtained from the Mallinckrodt Chemical Works, was used without further purification. The checkers used Baker and Adamson anhydrous diethyl ether purchased from the Industrial Chemicals Division of Allied Chemical Company.

7. The checkers found that this preparation was equally successful when a solution of 0.50 mole of diethyl isopropylidenemalonate in 100 ml. of diethyl ether was added over 25 minutes

to an ethereal solution of 0.55 mole of lithium dimethylcuprate. A solution of this reagent was prepared by adding 1.10 moles of methyllithium in diethyl ether solution (purchased from Foote Mineral Co., Exton, Pennsylvania) to a cold (−10°) suspension of 0.55 mole of copper(I) iodide in 200 ml. of anhydrous diethyl ether. The reaction mixture containing a suspension of yellow methylcopper was stirred at −5° for 5 minutes and then quenched into an aqueous mixture (pH 9) of ammonia and ammonium chloride. The product was isolated and distilled in the usual way to yield 100 g. (93%) of the diethyl *t*-butylmalonate, b.p. 57–61° (0.5–0.7 mm.), $n^{26.9}\text{D}$ 1.4224.

8. The hydroiodic acid liberated during the hydrolysis step is frequently oxidized to form iodine, which contaminates the final product. Washing the organic phase with aqueous sodium thiosulfate ensures the absence of iodine as an impurity in the final product.

9. The product has infrared absorption (CCl_4 solution) at 1750 cm.$^{-1}$ (ester C=O) with n.m.r. peaks (CCl_4 solution) at δ 4.05 (4 H quartet, $J = 7$ Hz.), 3.03 (1 H singlet), 1.22 (6 H triplet, $J = 7$ Hz.), and 1.08 (9 H singlet).

3. Discussion

Although diethyl *t*-butylmalonate may be prepared in low yield by the alkylation of diethyl sodiomalonate with *t*-butyl bromide[3] or *t*-butyl chloride,[4] the alkylation of active methylene compounds such as malonic esters with *t*-alkyl halides is normally a poor preparative procedure because of competing dehydrohalogenation of the alkyl halide.[5] A more satisfactory synthetic route to *t*-alkyl derivatives of malonic esters and related compounds consists of the conjugate addition of alkyl- or arylmagnesium halides to alkylidenemalonates or alkylidenecyanoacetates.[5,6] Thus diethyl *t*-butylmalonate has been prepared in yields of 37–64% by the conjugate addition of methylmagnesium iodide to isopropylidenemalonate.[7,8]

The addition of copper salts was found to favor the conjugate addition of Grignard reagents to alkylidenemalonic esters,[9] and Munch-Peterson subsequently found that the addition of 1 mole % of copper(I) chloride was generally useful for promoting the addition of Grignard reagents to α,β-unsaturated esters.[10] The preformed copper(I) reagents such as the ether-soluble lithium dialkyl- or diarylcuprates are even more effective reactants in conjugate additions to α,β-unsaturated carbonyl compounds.[11] The present preparation illustrates the use of copper(I) chloride to catalyze the addition of methylmagnesium iodide to an alkylidenemalonic ester. In this case high yields of the conjugate addition product are obtained either by this procedure or by the use of lithium dimethylcuprate (Note 7).

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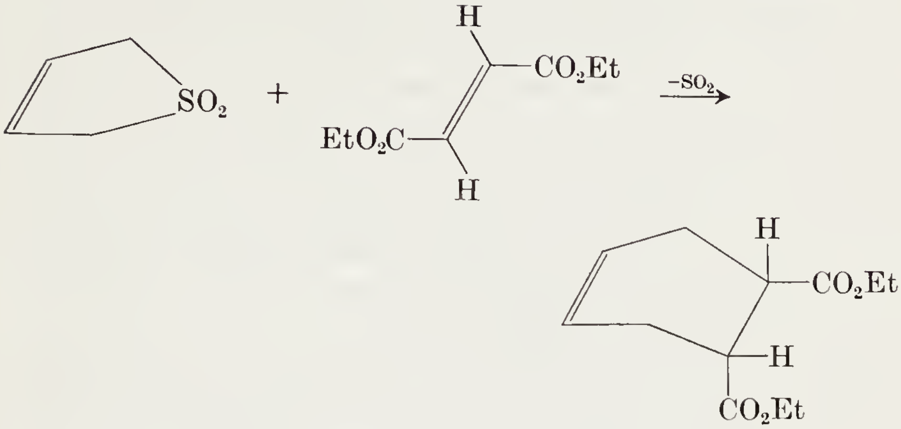
DIETHYL *trans*-Δ^4-TETRAHYDROPHTHALATE

(4-Cyclohexene-1,2-dicarboxylic acid, diethyl ester, *trans*-)



Submitted by Thomas E. Sample, Jr.,[1] and Lewis F. Hatch[2]
Checked by Elaine Dotter Donald and Richard E. Benson

1. Procedure

A pressure reaction vessel of about 300-ml. capacity capable of withstanding at least 250 p.s.i. at 125° (Note 1) is charged with 60.0 g. (0.51 mole) of 3-sulfolene (Note 2), 86.0 g. (82.0 ml., 0.50 mole) of diethyl fumarate (Note 3), and 1.0 g. of hydroquinone (Note 4). Commercial absolute ethanol (90 ml.) is added and the mixture stirred until most of the solid is dissolved. The vessel is sealed, heated slowly to 105–110° (Note 5), and maintained at that temperature 8–10 hours (Note 6). The vessel is then allowed to cool to room temperature, opened (Note 7), and the yellowish, fluid reaction mixture is poured into a 1-l. Erlenmeyer flask.

The liquid is stirred vigorously (Note 8), and a solution of 60.0 g. (0.57 mole) of sodium carbonate in 350 ml. of water is added to the flask as rapidly as the concomitant evolution of carbon dioxide will permit. Stirring is continued for about 15 minutes after the addition is complete. The original reaction vessel is rinsed with 200 ml. of petroleum ether (b.p. 60–75°) (Note 9), the rinse is added to the Erlenmeyer flask containing the product, and the mixture is stirred for about 10 minutes at a rate sufficient to achieve homogenization. The resulting loose emulsion is quickly transferred to a 1-l. separatory funnel and allowed to layer out; the lower (aqueous) phase is drawn off into the original Erlenmeyer flask and the upper (organic) layer containing the desired product is transferred to a 500-ml. flask. In exactly the same manner the aqueous phase is extracted by vigorous stirring twice with 100-ml. portions of petroleum ether, the organic layers being added to the retention flask (Note 10). The combined organic layers are transferred from the flask to the same separatory funnel and shaken once with 100 ml. of cold 5% aqueous sodium carbonate and twice with 50-ml. portions of cold water. The organic layer is returned to the retention flask and is dried over 10 g. of anhydrous magnesium sulfate. The drying agent is removed by gravity filtration. The petroleum ether is removed by distillation using a rotary film evaporator (Note 11), and the product is distilled through a Vigreux column under reduced pressure (Note 12). The yield of product, b.p. 129–132° (5 mm.,) is 75–82 g. (66–73%, based on diethyl fumarate); $n^{25}\text{D}$ 1.4565–1.4570, d_4^{25} 1.0584–1.0589 (Note 13).

2. Notes

1. The maximum static pressure developed at 110° measured by the submitters never exceeded 95 p.s.i.; however, for most of their runs they used stainless or carbon steel autoclaves with screw-on covers rated for service up to 500 p.s.i. at 250° (medium-pressure catalytic hydrogenation bombs). Gaskets or inner-disk seals for the autoclave covers were cut from soft thin copper sheet stock instead of the more usual lead or lead-alloy material. Whereas use of lead-containing seals did not seem to affect the yields, when they were used the product invariably had the offensive odor of divalent organic sulfur which was still noticeable after final distillation; substitution of copper seals eliminated this problem completely. Close-fitting, removable glass liners for the autoclave were used by the submitters for convenience in weighing and mixing the charge, and for subsequent removal of the product mixture, but are not required.

Several runs were made at 100–105° by the submitters without difficulty utilizing a hydrogenation bottle of heavy borosilicate glass tightly closed with a clamped-in Neoprene stopper and placed inside an iron sleeve for safety.

2. 3-Sulfolene (butadiene cyclic sulfone), m.p. 64–66°, from Shell Chemical Co., or from Aldrich Chemical Co., was found satisfactory for use as received. One lot purchased from another source required solution in hot methanol and treatment with activated carbon (250 ml. of methanol and 2 g. of Norit per 100 g. of material), filtration, and crystallization to free it of color, odor, and particulate matter.

3. Diethyl fumarate from Aldrich Chemical Co., $n^{20}\text{D}$1.4406, b.p. 97.5–97.7° (10 mm.), was employed without treatment.

4. Eastman Kodak Co. hydroquinone, m.p. 172–174°, was used. 4-*t*-Butylpyrocatechol, m.p. 38–42°, from the same supplier, proved to be an equally effective polymerization inhibitor.

5. The submitters used an ordinary hot-air oven with the usual simple bimetallic temperature regulator for the majority of their experiments. In several instances, however, a large oil bath thermostated to within ±1.0° was employed which, in providing more exact control of the total temperature environment of the reaction, gave a greater degree of reproducibility in product yield between successive runs at any set temperature; these precise runs were performed as a result of the checkers' observations emphasizing the important effect of reaction temperature on yields.

6. Longer heating periods (12–18 hours) were found by the submitters to elevate the yields only slightly. On the other hand, as the checkers noted, heating for the recommended 8–10 hours at temperatures above 110° will raise the yields quite significantly: the highest single product recovery obtained by the submitters was 86.8% using a strong steel autoclave (Note 1) immersed for 10 hours in the thermostated oil bath at 125°. However, the greater yield which may be realized through higher reaction temperatures should be carefully weighed by the user of this procedure against the ability of his available reaction vessel to contain safely the greater pressures developed.

7. Little, if any, overpressure is released if the vessel is opened below 30°; this should be done in a hood because the contents will evolve sulfur dioxide until the sodium carbonate is added.

8. A magnetic stirrer is recommended for this operation.

9. Hexane and Skellysolve-B serve equally well; the product is miscible with aliphatic solvents, whereas 3-sulfolene is not.

10. No increase in product recovery was observed by the submitters when a 72-hour exhaustive extraction of the neutralized reaction mixture with hexane in a continuous apparatus was substituted for the procedure described.

11. The submitters observe that no more critical step in this procedure exists than the efficient removal of the rather large quantity of solvent from the product before distillation: entrainment losses during this operation usually were found chiefly responsible when the synthesis gave a low yield (recovery). The preferred apparatus for this step is a rotary-film evaporator equipped with a long, helical, water-cooled condenser; the distillation flask is attached to the evaporator and the product solution added portionwise as the concentration progresses; the temperature of the flask is held at 30–40° with a warm-water bath, or a heat lamp, while the solvent is gently removed by a water aspirator down to about 30-mm. minimum pressure. If a suitable rotary evaporator is unavailable, a 30–45 cm. Vigreux column may be used without excessive product loss, providing the flask is warmed in the same manner and a gentle boiling rate is maintained through control of the aspirator suction.

12. An elaborate apparatus for the diminished-pressure distillation is not required to obtain a product of excellent purity: sensitive gas-chromatographic analyses could detect no more than a doubtful trace of the *cis* isomer in the crude mixture, and other possible contaminants boil at least 45° (760 mm.) below the product. The submitters usually employed an 8 × 300 mm., vacuum-jacketed, silvered column with a helical, Nichrome-wire heat transfer insert. They consistently obtained a product which analyzed at least 99% pure using vapor phase

chromatographic conditions proved capable of cleanly separating the product from an authentic sample of its *cis* isomer,[3] with the latter showing the longer retention time (terephthalic acid-terminated Carbowax 20M, 10% w/w on 60/80 mesh Chromosorb W, 6 mm. × 365 cm. aluminum column at 150°). The submitters note that distillation of the product at atmospheric pressure (b.p. 265–270°) is accompanied by very slight decomposition. (A b.p. of 150.5–151.5° at an unspecified pressure appears in the literature.[4])

13. The infrared spectra of diethyl *trans*-Δ^4-tetrahydrophthalate and its *cis*-isomer[3] (cm^{-1}, neat liquids purified by GLC, 0.025-mm. cells) are similar in the fundamental region; however, the following particular absorptions in the "fingerprint" region afford reliable analytical criteria for distinguishing each from (or in the presence of) the other; *trans* isomer, 971 (s), 755, 743 (m, s, doublet); *cis* isomer, 945 (s), 893 (w), 727 (m). The 755, 743 doublet of the *trans* isomer and the 727 single absorption of the *cis* isomer appear to be characteristic, and related to out-of-plane deformations of the vinylic hydrogens; bands corresponding to the 971 and 755, 743 absorptions of the *trans* isomer are present also in the spectrum of dimethyl *trans*-Δ^4-tetrahydrophthalate.[5]

3. Discussion

A report of Backer and Blaas[6] is responsible for evolution of the present procedure; these workers were first to conduct a Diels-Alder synthesis utilizing a 3-sulfolene in place of the free diene (by heating the cyclic adduct of sulfur dioxide and 2-methyl-3-thiomethyl-1,3-butadiene with maleic anhydride). The generality of the method as a variant of the conventional diene synthesis is limited largely by the availability of the appropriate 3-sulfolene; its greatest utility, perhaps, will be presently realized in those diene reactions normally requiring 1,3-butadiene, since 3-sulfolene itself is now the least expensive and most widely available diene cyclic sulfone.

The submitters, in addition to their successful work with 3-sulfolene itself, have generally obtained very satisfactory results performing diene syntheses based on the present procedure using several fumaric and maleic derivatives (notably fumaric acid and fumaronitrile, and diethyl maleate) in conjunction with 3-methyl-3-sulfolene (isoprene cyclic sulfone)[7] and 2,4-dimethyl-3-sulfolene (available from Aldrich Chemical Co.), as well as 3,4-dimethyl-3-sulfolene.[8]

In preparations wherein the dienophile could undergo side reaction with the solvent alcohol, either benzene or toluene usually proved to be a satisfactory reaction medium; lower-boiling solvents, such as ether, chloroform, or acetone, were avoided by the submitters because of the high reaction pressures developed. If the dienophile is highly reactive and not appreciably volatile below about 200°, the reaction may be successfully conducted without solvent by careful fusion of an intimate mixture of the reactants in an open vessel.[6,9] *Caution! Such fusions should be performed in a good fume hood because of the copious evolution of sulfur dioxide.*

3-Sulfolene as an alternative reactant for 1,3-butadiene in diene syntheses has the following advantages: it presents no particular flammability hazard[10] and is practically nontoxic[11]; it is an odorless, crystalline, nonhygroscopic solid which may be stored without inhibitor at ordinary temperatures for years and show no evidence of deterioration[11]; obviously, no low-temperature liquefication procedures are needed for its handling such as butadiene may require; medium-pressure reaction vessels can be safely employed since autogenous pressures during its use are relatively low owing to the thermally controlled release of the 1,3-butadiene[12]; and, because the substantial excess of free diene often employed to force the usual reaction is not required, formation of troublesome polymeric by-products is greatly diminished.

For the preparation of diethyl *trans*-Δ^4-tetrahydrophthalate, the present synthesis is superior to the Diels-Alder reaction of butadiene with diethyl fumarate[4] for the reasons given above. In addition, a higher yield is obtained at a lower reaction temperature and shorter reaction time.

Whereas *cis*-Δ^4-tetrahydrophthalic anhydride and several of its derivatives are readily available in high purity from a number of suppliers (largely because of the great ease of addition of maleic anhydride to 1,3-butadiene[3]), the *trans* analogs are much more difficult and expensive to prepare and isolate in reasonable yields and purity; hence the latter are rarely procurable at present from the usual laboratory supply sources. Thus the procedure described for the preparation of high-purity diethyl *trans*-Δ^4-tetrahydrophthalate not only illustrates a useful variation of the diene synthesis, it also provides a convenient route to a large number of *trans*-1,2-disubstituted cyclohexyl derivatives that are presently difficult to secure and which are of importance for a variety of active studies concerned with structural problems.

1. Texaco Inc., Bellaire Research Laboratories, Bellaire, Texas 77401
2. School of Science, The University of Texas, El Paso, Texas 79999. This work was supported in part by a grant from the Robert A. Welch Foundation and carried out in the Department of Chemistry at The University of Texas, Austin, Texas 78712.
3. A. C. Cope and E. C. Herrick, *Org. Syntheses*, Coll. Vol. **4**, 304 (1963).
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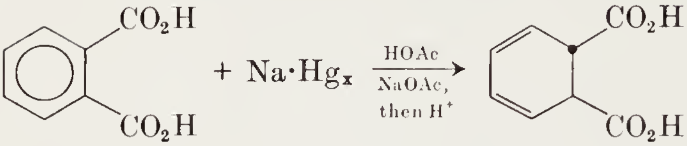
11. Technical Information Bulletin PD-146, "3-Sulfolene", Shell Chemical Company, Industrial Chemicals Division, New York, N.Y. 10020, 1963, pp. 2, 10.
12. L. R. Drake, S. C. Stowe, and A. M. Partansky, *J. Amer. Chem. Soc.*, **68**, 2521 (1946); O. Grummitt, A. E. Ardis, and J. Fick, *J. Amer. Chem. Soc.*, **72**, 5167 (1950).

trans-1,2-DIHYDROPHTHALIC ACID

(3,5-Cyclohexadiene-1,2-dicarboxylic acid)



Submitted by Richard N. McDonald and Charles E. Reineke[1]
Checked by Herbert A. Kirst and E. J. Corey

1. Procedure

A vigorously stirred particle-free (Note 1) solution of 170 g. (1.02 moles) of phthalic acid and 281 g. of sodium acetate in 1.7 l. of water is cooled in an ice bath while a total of 3400 g. of 3% sodium amalgam (Note 2) is added in 50–100 g. portions (Note 3). With each portion of added amalgam there is also added 10–20 ml. (500 ml. total) of 50% acetic acid. The total addition time required is 4–5 hours. The solution is decanted from the mercury onto a Buchner funnel and filtered with suction through a layer of Celite 545. The cold filtrate is treated with 1.7 l. of cold 20% sulfuric acid. Crystallization of the acid begins immediately. After standing for 4 hours at 20–22°, the acid is collected by suction filtration, washed well with ice-cold water to remove excess sulfuric acid, and dried in a vacuum desiccator over sulfuric acid to give 124 g. (72%) of crystalline product, m.p. 210–213°. A purer product can be obtained by recrystallization. For minimum losses during recrystallization, the crude acid is divided into two portions and each is added to 1.2–1.5 l. of rapidly stirred, boiling water to effect as rapid a solution as possible. When almost all of the solids have dissolved *ca.* 1 g. of activated charcoal (Norit) is added, the solution is filtered through a fluted filter, and the filtrate is cooled in ice to induce rapid crystallization (Note 4). The colorless crystals are collected by filtration and dried under reduced pressure to yield 93–107 g. (54–62%) of the acid, m.p. 212–214°.

2. Notes

1. If any crystals of phthalic acid are present, crystallization will occur on cooling.

2. The 3% sodium amalgam was prepared by the procedure in *Org. Syntheses* Coll. **2**, 609, (1943), Note 3, with the following explanation. The mineral oil and sodium are placed in a 1-l. heavy-wall filter flask and heated on a hot plate until the sodium is molten. To this hot, strongly swirled mixture is added the mercury from a 1-l. separatory funnel. The initial amounts of mercury (about ¼ the total) are added in a fine steady stream, gradually increasing the rate of flow as the initial crackling ceases. Fire flashes can be observed if the initial addition is too rapid. Once the initial reaction subsides, the mercury should be added as rapidly as possible, and about the last third can be essentially poured in. The molten amalgam is *immediately* poured into a shallow porcelainized metal pan and stirred with a wide spatula so that large chunks are not allowed to form as the amalgam cools. Once cool, the amalgam pieces are washed repeatedly with petroleum ether to remove the mineral oil.

3. Another portion of amalgam and one of acid are added as soon as the gas evolution from the previous addition subsides.

4. The submitters report that treatment with decolorizing carbon may not be necessary. Although the crude product is invariably colorless, a yellow color develops during the recrystallization procedure. The checkers found that without decolorization a yellow product of somewhat lower m.p. was obtained.

3. Discussion

The present method, based on a recent publication,[2] is a modification of that previously reported.[3] *trans*-1,2-Dihydrophthalic acid has been converted to the *cis*-anhydride by heating in acetic anhydride[2] which on photolysis (Hanovia, type L mercury lamp) yields the photo-anhydride, bicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic anhydride.[2,4] The photo-anhydride has been converted to bicyclo[2.2.0]hexa-2,5-diene,[4] bicyclo[2.2.0]hex-2-ene,[2] and *exo*-bicyclo[2.2.0]hexan-2-ol[2] as well as certain derivatives of the alcohol. The present procedure also gives a more complete preparation of 3% sodium amalgam.

1. Department of Chemistry, Kansas State University, Manhattan, Kansas 66502.
2. R. N. McDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967).
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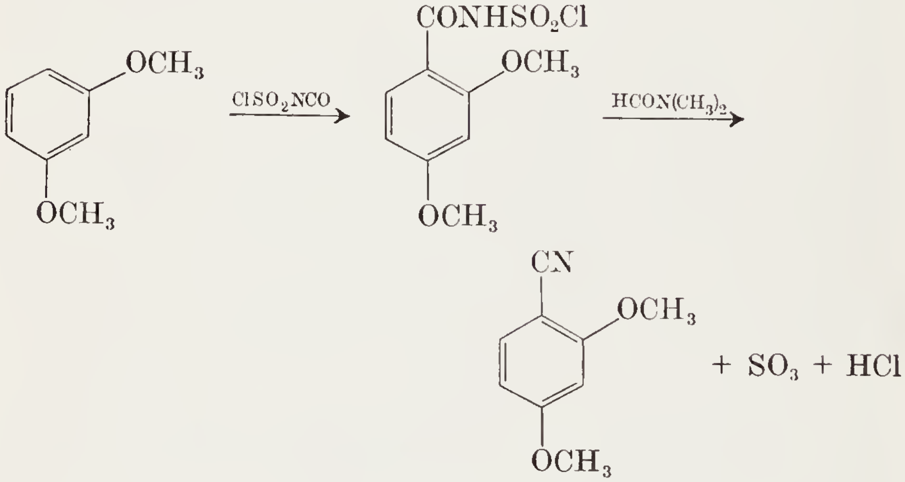
4. E. E. van Tamelen and S. P. Pappas, *J. Amer. Chem. Soc.*, **85**, 3297 (1963)

2,4-DIMETHOXYBENZONITRILE

(Benzonitrile, 2,4-dimethoxy-)



Submitted by G. Lohaus[1]
Checked by Jurgen K. Weise and Richard E. Benson

1. Procedure

Caution. Chlorosulfonyl isocyanate is a highly corrosive, irritating compound. This reaction should be carried out in an efficient hood.

A 1-l. round-bottomed flask is equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser to which is attached a drying tube containing calcium chloride. Resorcinol dimethyl ether, 131 ml. (138 g., 1.0 mole) and 200 ml. of methylene chloride are added to the flask. The solution is stirred, and a solution of 150 g. (1.06 moles) of chlorosulfonyl isocyanate (Note 1) in 100 ml. of methylene chloride is added with stirring at 15–20° during a 25-minute period. The amide N-sulfonyl chloride separates as a crystalline solid, and the mixture is stirred for an hour at room temperature. The resulting mixture is cooled to 10–12° (Note 2) and 154 g. (2.1 moles) of dimethylformamide (Note 3) is added during a period of 5 minutes. The cooling bath is removed and the temperature gradually rises to about 30° and then falls. After 1 hour the crystals have dissolved and the reaction mixture is poured onto 200 g. of ice. After the ice has melted, methylene chloride (150 ml.) is added, the mixture is shaken, and the organic layer is separated. The aqueous layer is extracted with 100 ml. of methylene chloride, and the organic phases are combined and washed with 100 ml. of water. The methylene chloride is removed by distillation to yield a white solid that is triturated with 250 ml. of cold water, recovered by filtration, and dried. The yield of 2,4-dimethoxybenzonitrile is 155–157 g. (95–96%), m.p. 91°. Gas liquid chromatography using a Chromosorb W column with 10% butadiene sulfone as the stationary phase indicates that the product has a purity of 98%. The infrared spectrum shows absorption at 4.5 μ attributable to the cyano group.

2. Notes

1. R. Graf, *Org. Syntheses*, **46**, 23 (1966). Chlorosulfonyl isocyanate is available from Farbwerke Hoechst AG. The checkers found it necessary to distill the product before use.

2. A less pure product is obtained if the temperature is allowed to rise at this phase of the reaction.

3. Other amides also can be used, but dimethylformamide generally is preferred, especially because of its low molecular weight, high solvent power, and miscibility with water. In addition, it is readily available.

3. Discussion

This procedure[2] is an example of a broadly applicable, simple method for introducing the cyano substituent into compounds that readily undergo electrophilic substitution. The method is characterized by mild reaction conditions, simple workup procedure, and, in most cases, good yields. Although the method comprises two reaction steps, the reaction generally can be carried out without isolation of the intermediate chlorosulfonamide. An indication of its scope is given in Table I.[2] Additional examples of the substitution reaction of chlorosulfonyl isocyanate with aromatic and heterocyclic compounds and with olefins to yield carboxylic acid amide N-sulfonyl chlorides are reported.[2–6]

TABLE I

Nitriles[2] Prepared from $ClSO_2NCO$

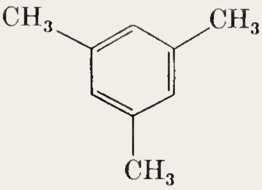
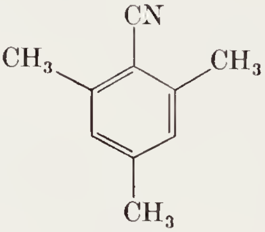
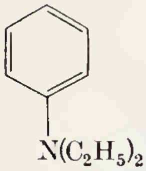
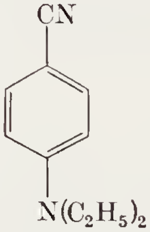
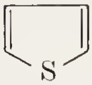
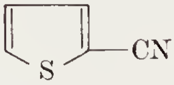
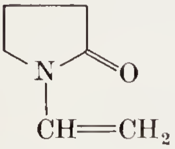
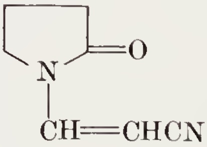
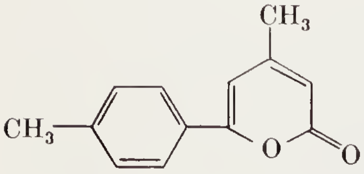
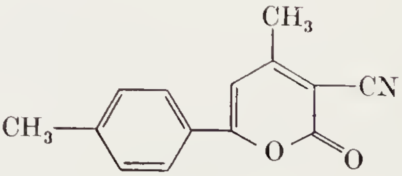
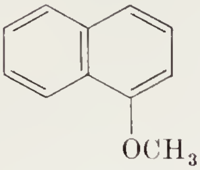
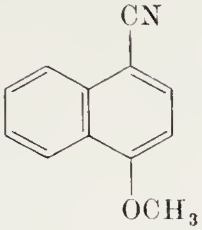
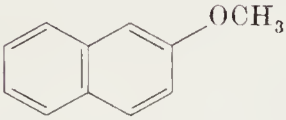
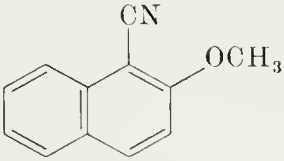
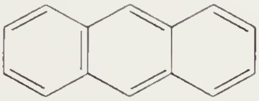
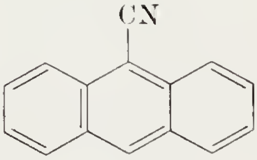
Reactant	Product	Yield, %
		67
		20
		66
		86
		84

TABLE I (*continued*)

Reactant	Product	Yield, %
		81
		95
		89

Other procedures for the preparation of 2,4-dimethoxybenzonitrile include the reaction of 2,4-dimethoxybenzamide with thionyl chloride,[3] the action of acetic anhydride on 2,4-dimethoxybenzaldoxime,[7] the reaction of diazotized 2,4-dimethoxyaniline with potassium copper cyanide,[8] and the action of cyanogen bromide on resorcinol dimethyl ether in the presence of aluminum chloride.[9]

1. Farbwerke Hoechst AG., vormals Meister Lucius und Brüning, Frankfurt/Main-Höchst, Germany.
2. G. Lohaus, *Chem. Ber.*, **100**, 2719 (1967).
3. F. Effenberger, R. Gleiter, L. Heider, and R. Niess, *Chem. Ber.*, **101**, 502 (1968).
4. R. Graf, *Ann. Chem.*, **661**, 111 (1963).
5. M. Seefelder, *Chem. Ber.*, **96**, 3243 (1963).
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7. H. Baganz and I. Paproth, *Naturwiss.* **40**, 341 (1953).
8. E. Späth, K. Klager, and C. Schlösser, *Ber. Deut. Chem. Ges.*, **64**, 2203 (1931).
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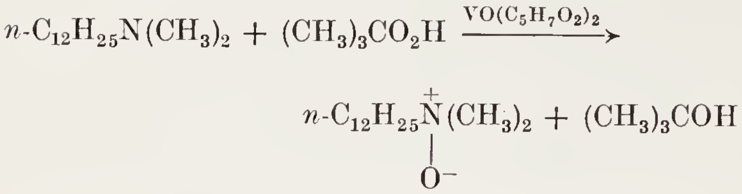
N,N-DIMETHYLDODECYLAMINE OXIDE

(Dodecylamine, *N,N*-dimethyl; *N*-oxide)



$$n\text{-}C_{12}H_{25}N(CH_3)_2 + (CH_3)_3CO_2H \xrightarrow{VO(C_5H_7O_2)_2} n\text{-}C_{12}H_{25}\overset{+}{N}(CH_3)_2 + (CH_3)_3COH$$

$$\underset{O^-}{|}$$

Submitted by M. N. Sheng and J. G. Zajacek[1]
Checked by William F. Fischer, Jr., and Herbert O. House

1. Procedure

A solution of 21.3 g. (0.10 mole) of freshly distilled N,N-dimethyldodecylamine (Note 1), 9.6 g (0.10 mole) of 94% *t*-butyl hydroperoxide (Note 2), and 0.050 g. of vanadium oxyacetylacetonate (Note 3) in 27 g. (34 ml.) of *t*-butyl alcohol is placed in a 250-ml. round-bottomed flask fitted with a thermometer, a reflux condenser, and a heating mantle. The reaction mixture is heated to approximately 65–70°, at which point an exothermic reaction begins. The heating is discontinued until the vigorous exothermic reaction subsides (about 5 minutes) and then the reaction mixture is heated at reflux (the reaction mixture boils at 90°) for 25 minutes. After the resulting mixture has been cooled to room temperature, *it is analyzed* (Note 4) *to establish the absence of t-butyl hydroperoxide*, and then concentrated with a rotary evaporator (30–35° bath with 30–40 mm. pressure). The crude solid residue is triturated with 50 ml. of cold (0–5°), anhydrous diethyl ether and then filtered under conditions which prevent exposure of the residual amine oxide to atmospheric moisture (Note 5). The residual solid is washed with 50 ml. of cold (0–5°) anhydrous diethyl ether and then dried under reduced pressure to leave 12.9–15.5 g. of the crystalline amine oxide, m.p. 131–131.5°. Concentration of the mother liquors and trituration of the residual paste with 25 ml. of cold (0–5°) anhydrous diethyl ether separates another 4.9–3.4 g. of the amine oxide, m.p. 130–131°. The total yield of the crystalline amine oxide (Note 6) is 17.4–18.9 g. (76–83%).

2. Notes

1. N,N-Dimethyldodecylamine purchased from Eastman Organic Chemicals is approximately 90% pure. This material should be fractionally distilled with a spinning band column to obtain the pure amine, b.p. 116–117° (4 mm.).

2. *t*-Butyl hydroperoxide purchased from the Lucidol Division, Wallace and Tiernan, Inc., is approximately 92% pure. A portion of the major impurity, water, can be removed by drying the commercial material over anhydrous magnesium sulfate for 2 days to leave material that is 94–97% pure.

3. Vanadium oxyacetylacetonate may be purchased from Alfa Inorganics, Inc., Beverly, Massachusetts.

4. Although consumption of the hydroperoxide is normally complete, the absence of this peroxide in the reaction mixture should be established by testing with moist starch-iodide paper or by iodometric titration.[2] The amine oxide content may be determined by titration with standard aqueous hydrochloric acid after any amine present has been consumed by reaction with methyl iodide for 1 hour at room temperature.[3] From this volumetric analysis the submitters determined the yield of amine oxide to be 86%. The checkers found that the reaction could be followed by measuring the n.m.r. spectra in *t*-butyl alcohol solution where the n.m.r. N-methyl signals of the amine (at δ 2.03) and the amine oxide (at δ 2.98) are readily observed.

5. The amine oxide is exceedingly hygroscopic and must be protected from atmospheric moisture during this filtration. The submitters found it convenient to use a Buchner funnel covered with a large, inverted rubber stopper. After the mixture of amine oxide and ether is added to the funnel, the mouth of the funnel is covered with the inverted rubber stopper and suction is applied. The flat surface of the inverted rubber stopper forms a seal against the mouth of the funnel, preventing the entrance of moist air while the last traces of ether are removed under reduced pressure. The checkers employed a sintered-glass funnel fitted to maintain a nitrogen atmosphere above the crystalline product.

6. The hygroscopic amine oxide should be protected from

moisture during storage. The checkers found that the initial product could be recrystallized from toluene under anhydrous conditions to yield the amine oxide as white needles, m.p. 130–131°.

3. Discussion

Aqueous or alcohol solutions of amine oxides are normally obtained by oxidizing tertiary amines with either hydrogen peroxide or a peracid.[4] For example, N,N-dimethyldodecylamine oxide has been prepared by treating N,N-dimethyldodecylamine with aqueous hydrogen peroxide.[5] The procedure illustrated in this preparation permits the oxidation of tertiary amines with *t*-butyl hydroperoxide in organic solvents under relatively anhydrous conditions.[6] In this procedure the reaction time is short and the method is as convenient as the use of aqueous hydrogen peroxide or a peracid as the oxidant. Furthermore, isolation of the anhydrous amine oxide is often relatively simple.

1. The Research and Development Department, ARCO Chemical Company, A Division of Atlantic Richfield Company, Glenolden, Pennsylvania.
2. D. H. Wheeler, *Oil & Soap*, **9**, 89 (1932) [*C.A.*, **26**, 3128 (1932)].
3. L. D. Metcalfe, *Anal. Chem.*, **34**, 1849 (1962).
4. A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 378 (1960).
5. G. L. K. Hoh, D. O. Barlow, A. F. Chadwick, D. B. Lake, and S. R. Sheeran, *J. Amer. Oil Chem. Soc.*, **40**, 268 (1963).
6. M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **33**, 588 (1968).

2,2-DIMETHYL-4-PHENYLBUTYRIC ACID

$$(CH_3)_2CHCO_2Na + LiN[CH(CH_3)_2]_2 \rightarrow [(CH_3)_2CCO_2]^{2-}\ Li^+Na^+$$

$$[(CH_3)_2CCO_2]^{2-}\ Li^+Na^+ + C_6H_5CH_2CH_2Br \rightarrow C_6H_5CH_2CH_2C(CH_3)_2CO_2H$$

Submitted by P. L. Creger[1]
Checked by Paul Kalicky and Ronald Breslow

1. Procedure

A 500-ml. three-necked flask is equipped with a mechanical stirrer and a two-necked adapter carrying a Friedrich condenser, and a thermometer which contacts the flask contents.

The third neck of the flask carries a pressure-equalized dropping funnel which is exchanged for a serum stopple as required. The condenser is attached to a suitable source of nitrogen. The reaction flask is placed in a heating mantle and then it is charged with 7.75 g. (0.075 mole) of diisopropylamine (Note 1), 3.68 g. (0.0825 mole) of 54% sodium hydride in mineral oil (Note 2), and 75 ml. of tetrahydrofuran (Note 3). To the stirred mixture is added from the dropping funnel over 5 minutes 6.6 g. (0.075 mole) of isobutyric acid (Note 4). The internal temperature rises to 50–60° and hydrogen evolution is completed by heating the mixture to reflux for 15 minutes. After cooling to 0° by means of an externally applied ice-salt bath (Note 5), 52 ml. of a standard solution of *n*-butyllithium in heptane (1.45 mmole/ml.; 0.075 mole) (Note 6) is added through the stopple by injection (Note 7) at a temperature below 10°. The ice bath is retained for 15 minutes and then the mixture is heated to 30–35° for 30 minutes to complete the metalation. The turbid solution which results is cooled and 13.9 g. (0.075 mole) of (2-bromoethyl) benzene (Note 8) is added from the dropping funnel over 20 minutes at 0°. A colorless precipitate of sodium bromide begins to separate almost immediately. The ice bath is retained for 30 minutes, after which the mixture is heated to 30–35° for 1 hour.

At the conclusion of the reaction period, 100 ml. of water is added at a temperature below 15° (Note 9). The aqueous layer is separated and the reaction flask and organic layer are washed with a mixture of 50 ml. of water and 75 ml. of ether. The aqueous layers are combined, back-extracted with 50 ml. of ether, and acidified to Congo red with 6 *N* hydrochloric acid, and the product is extracted with two 75-ml. portions of ether. The ether solution of product is washed with 50 ml. of saturated sodium chloride and dried over anhydrous magnesium sulfate, and the solvent is evaporated. The remaining traces of solvent may be removed in a rotary evaporator. The crude 2,2-dimethyl-4-phenylbutyric acid amounts to 12–12.8 g. (83–90%), m.p. 89–94°, which is suitable for many purposes. Recrystallization from 75 ml. of hexane at room temperature followed by refrigeration yields 8.4–9.7 g. (58–67%) of product as colorless needles, m.p. 98–99.5° (Note 10). Recrystallization of the filtrate residue from 20 ml. of hexane yields a small second crop amounting to 1.2–1.6 g. (8–11%), m.p. 95–97°. The combined yield amounts to 10–11 g. (70–76%) (Note 11).

2. Notes

1. Diisopropylamine supplied by Matheson, Coleman and Bell was distilled from calcium hydride, b.p. 83–85°.

2. Sodium hydride supplied by Ventron Corp. is satisfactory. It is unnecessary to remove the mineral oil.

3. Tetrahydrofuran was obtained in drum quantities from E. I. duPont de Nemours Co. and was transferred under nitrogen pressure to 1-gallon containers for stock. This material could be used without special treatment. The quality of the tetrahydrofuran should be determined [*Org. Syntheses*, **46,** 105 (1966)] if there is no assurance of the absence of gross contamination. A small excess of sodium hydride was used in the reaction to remove traces of moisture which may have been introduced during measurement.

4. Isobutyric acid supplied by Matheson, Coleman and Bell is satisfactory.

5. A brisk nitrogen flow is required to exclude air when cooling.

6. *n*-Butyllithium in 1-mole serum cap bottles from Foote Mineral Co. was used. The less volatile hexane or heptane solutions were preferred.

7. The *n*-butyllithium solution was forced into a 100-ml. syringe through a $1\frac{1}{2}$-in., 19 gauge hypodermic needle by slightly pressurizing ($\frac{1}{2}$ to $1\frac{1}{2}$ p.s.i.) the storage bottle with nitrogen. Nitrogen was admitted through a second, 2-in., 20 gauge needle inserted at an upward angle through the stopper into the void space of the inclined bottle. The pressure in the bottle should be released and the bottle should be returned to an upright position before the syringe is withdrawn. This operation should be conducted from behind a safety shield.

8. (2-Bromoethyl)benzene was used as supplied by Matheson, Coleman and Bell.

9. At the beginning, water should be added cautiously since a small quantity of unreacted sodium hydride is present.

10. The literature[2–7] reports m.p. 97–98°.

11. N.M.R. analysis of the filtrate residue indicates that it is *ca.* 90% product. The submitters carried out the procedure on four times this scale, with mechanical stirring.

3. Discussion

2,2-Dimethyl-4-phenylbutyric acid has been prepared by Clemmensen reduction[2–6] or by hydriodic acid, phosphorus reduction[7] of 3-benzoyl-2,2-dimethylpropionic acid, and by catalytic reduction[6] of 2,2-dimethyl-4-phenyl-3-butenoic acid.

The preparation of 2,2-dimethyl-4-phenylbutyric acid is a specific example of a generally applicable procedure for alkylating dialkylacetic acids. The present procedure represents an improvement on one described earlier[8] in that one equivalent of *n*-butyllithium is required. Sufficient experience has been accumulated by the submitter over several years to recommend the present method as a possible alternative to the multistep Haller-Bauer sequence.[9] The procedure offers the obvious advantages of being short, avoiding use of blocking groups for the carboxyl group which must be removed later, and affording ease of workup while still providing preparative yields of product. The scale of the reaction can be increased to 1–2 moles with only a moderate increase in the size of the equipment.

The same procedure has been used to monoalkylate alkylacetic acids[10] and it may be used to selectively monoalkylate methylated benzoic acids.[11] The metalated intermediates generated from alkylacetic acids are generally less soluble in the reaction medium specified, and heterogeneous mixtures result. The physical state of the reaction mixture has no apparent effect on the success of the succeeding alkylation[10] so long as metalation is complete. Homogeneous solutions may be obtained at the expense of operational convenience by suitable changes in the cation used,[11,12] or by use of hexamethylphosphoramide as cosolvent.[12,13]

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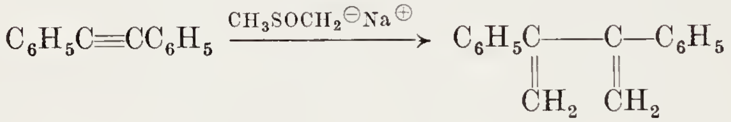
2,3-DIPHENYL-1,3-BUTADIENE

(1,3-Butadiene, 2,3-diphenyl)

$$2\,CH_3SOCH_3 + 2\,NaH \rightarrow 2\,CH_3SOCH_2^{\ominus}Na^{\oplus} + 2\,H_2$$



$$C_6H_5C{\equiv}CC_6H_5 \xrightarrow{CH_3SOCH_2^{\ominus}Na^{\oplus}} C_6H_5C(=CH_2)\text{—}C(=CH_2)\text{—}C_6H_5$$

Submitted by Issei Iwai and Junya Ide[1]
Checked by James B. Sieja and Richard E. Benson

1. Procedure

A 300-ml. three-necked round-bottomed flask is fitted with a sealed mechanical stirrer, a thermometer, and a reflux condenser to which is attached a T-tube connected to a source of pure nitrogen. The remaining joint of the T-tube is connected to a bubbling device so that the rate of nitrogen flow can be observed throughout the course of the reaction. The flask is flushed with nitrogen and 30 ml. of anhydrous dimethyl sulfoxide (Note 1) and 2.4 g. of about 50% sodium hydride in oil (about 0.05 mole) (Note 2) are added. Stirring is begun and the contents of the flask are heated to 75° for 30 minutes (Note 3) under a slight pressure of nitrogen. The flask is cooled in a water bath to 30°, and to the dark gray solution is added dropwise with stirring at 30° a solution of 4.45 g. (0.025 mole) of diphenylacetylene (Note 4) in 20 ml. of anhydrous dimethyl sulfoxide. During the addition the temperature of the reaction mixture gradually rises and at the end of the addition it reaches about 40°. After the addition is completed, the reaction mixture is heated to 65° and held at this temperature for 2.5 hours. The resulting red-brown reaction mixture is cooled to room temperature and poured onto 500 ml. of an ice and water mixture with stirring. After the ice has melted, the mixture is extracted five times with 150 ml. portions of ether. The ether extractions are combined and washed with three 100-ml. portions of water and then dried over sodium sulfate. The ether is removed by distillation at reduced pressure and the product (about 6.0 g.) is chromatographed on 180 g. of alumina (Note 5). The elution is begun with the solvent system of benzene:*n*-hexane (1:7) and ten fractions of 50 ml. of eluate are collected. The first two fractions contain almost all of the mineral oil that was originally present in the sodium hydride reagent. Fractions 3 through 8 are combined and the ether removed by distillation to yield 1.2–1.4 g. (22–25%) of slightly impure 2,3-diphenyl-1,3-butadiene (Note 6). Recrystallization from methanol gives 0.55–0.70 g. (10.7–13.6%) of pure 2,3-diphenyl-1,3-butadiene, m.p. 47–48° (Note 7).

The n.m.r. spectrum (60 MHz., carbon tetrachloride solvent with tetramethylsilane as an internal reference) shows a complex multiplet centered at 431 Hz. attributable to the aromatic protons, and two doublets centered at 326 and 313 Hz., respectively, attributable to the olefinic protons.

2. Notes

1. Commercially available dimethyl sulfoxide is freshly distilled in the presence of calcium hydride, b.p. 56–57° (5 mm.).

2. Sodium hydride in oil (about 50%), available from Metal Hydrides Inc., Beverly, Massachusetts, was used.

3. The formation of methylsulfinyl carbanion is essentially complete at this time.

4. The preparation of diphenylacetylene is described in

Organic Syntheses.[2] The checkers purchased it from Eastman Organic Chemicals.

5. Aluminum Oxide Woelm neutral, activity grade 1, available from M. Woelm, Eschwege, Germany, was used. The column dimensions were 2.9 cm. × 29 cm., and the alumina was placed in the column with *n*-hexane.

6. This grade of 2,3-diphenyl-1,3-butadiene is satisfactory for most purposes.

7. Crude 2,3-diphenyl-1,3-butadiene is unstable. The pure product should be stored in the dark in a refrigerator. The submitters have found it to be stable for at least one year under these conditions.

3. Discussion

This method provides a simple one-step synthesis of 2,3-diphenyl-1,3-butadiene from the readily available diphenylacetylene. It illustrates an unusual reaction that has been relatively uninvestigated. The scope of the reaction is unknown, but it would appear that the procedure could be applied to disubstituted acetylenes having aryl substituents that contain functionality that is unaffected by the strong basic conditions of the reaction.

A conventional preparation of 2,3-diphenyl-1,3-butadiene involves dehydration of *meso*-2,3-diphenyl-2,3-butanediol by acidic reagents including acetic anhydride,[3–5] acetyl bromide,[5] sulfanilic acid,[6] and potassium hydrogen sulfate.[7] Other procedures have been summarized[2] previously.

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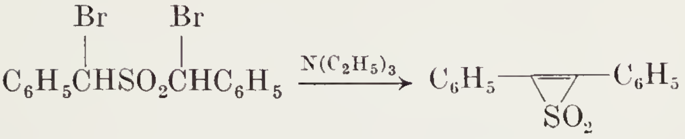
2,3-DIPHENYLVINYLENE SULFONE

(Thiirene, diphenyl-, 1,1-dioxide)



Submitted by Louis A. Carpino and Louis V. McAdams, III[1]
Checked by Timothy P. Higgs and Ronald Breslow

1. Procedure

To a magnetically stirred solution of 6.36 g. (0.0157 mole) of crude α,α′-dibromodibenzyl sulfone[2] (m.p. 135–150°) in 40 ml. of methylene dichloride contained in a 100-ml. round-bottomed flask fitted with a reflux condenser there is added in one portion 5.05 g. (0.05 mole) of triethylamine. The solution is heated at reflux with stirring for 3 hours (Note 1), filtered, and the precipitate washed with 5 ml. of cold (0°) methylene dichloride. The combined methylene dichloride solution is washed with two 20-ml. portions of 3 *N* hydrochloric acid followed by one 10-ml. portion of water. Removal of the solvent by distillation from a water bath at 30° with the aid of a water aspirator gave 3.0 g. (80%) of the vinylene sulfone as a tan solid, m.p. 116–126° (dec.). The crude solid is washed with 5 ml. of cold (0°) ethanol and recrystallized from about 10 ml. of benzene to give 2.4–2.5 g. (63–67%) of the pure sulfone as tiny snow-white needles, m.p. 123–126° (dec.) (Note 2).

2. Notes

1. After about 45 minutes the triethylamine hydrobromide began to precipitate.
2. The submitters obtained a similar percent yield on ten times the scale.

3. Discussion

2,3-Diphenylvinylene sulfone has been prepared only from α,α′-dibromodibenzyl sulfone.[3] The procedure illustrates a general technique for the synthesis of diarylvinylene sulfones, a group of compounds of considerable theoretical interest.[3,4]

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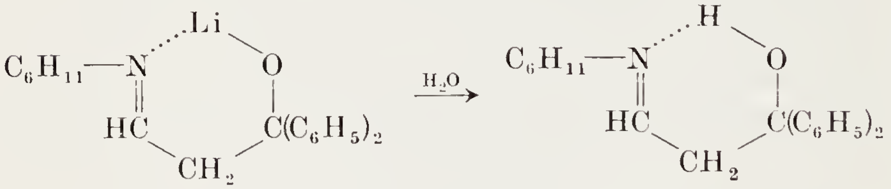
DIRECTED ALDOL CONDENSATIONS. β-PHENYLCINNAMALDEHYDE

(Acrolein, 3,3-diphenyl)

$$C_6H_{11}NH_2 + CH_3CHO \xrightarrow[-H_2O]{Na_2SO_4} C_6H_{11}N{=}CHCH_3$$

$$\xrightarrow[-(i\text{-}C_3H_7)_2NH]{(i\text{-}C_3H_7)_2NLi,\ (C_2H_5)_2O} C_6H_{11}N{=}CHCH_2Li \xrightarrow[(C_2H_5)_2O,\ 25°]{(C_6H_5)_2CO}$$



$$\xrightarrow[H_2O,\ 100°,\ -C_6H_{11}NH_2]{(CO_2H)_2} (C_6H_5)_2C{=}CHCHO$$

Submitted by G. Wittig and A. Hesse[1]
Checked by Allan Y. Teranishi and Herbert O. House

1. Procedure

A. *Ethylidenecyclohexylamine.* A dry 500-ml. round-bottomed flask fitted with a magnetic stirrer is flushed with nitrogen and then stoppered with a rubber septum. To the flask is added from a hypodermic syringe 99.2 g. (1.00 mole) of freshly distilled cyclohexylamine (b.p. 133–134°). After the amine has been cooled to approximately −20° (Note 1) with a dry ice-acletone bath, 44.1 g. (1.00 mole) of freshly distilled acetaldehyde (b.p. 21°) is added from a hypodermic syringe dropwise and with stirring over a 15-minute period. During the initial phase of this addition a white solid separates but redissolves as the addition is continued. The resulting cold solution is stirred at −20° for approximately 45 minutes, at which time a large amount of white solid separates and further stirring is impractical. The resulting mixture is allowed to stand at −20° for 15 minutes and then 15 g. of anhydrous sodium sulfate is added and the mixture is allowed to melt and warm to room temperature. The resulting mixture is filtered with gravity and the residue is washed with approximately 15 ml. of ether. The combined filtrates are dried further over 5 g. of anhydrous magnesium sulfate and filtered. The filtrate is distilled under reduced pressure to separate 95–99 g. (76–79%) of ethylidenecyclohexylamine as a colorless liquid, b.p. 47–48° (12 mm.) or 54–55° (16 mm.), n^{20}D 1.4579; n^{25}D 1.4560. This product should either be used immediately in the next step or stored in a refrigerator (5–10°) under a nitrogen atmosphere.

B. 3-*Hydroxy*-3,3-*diphenylpropylidenecyclohexylamine.* A dry 250-ml. round-bottomed flask or dry 250-ml. Schlenk tube fitted with a magnetic stirrer is flushed with oxygen-free nitrogen (Note 2), stoppered with a rubber septum, and cooled in an ice bath. A slight positive pressure of oxygen-free nitrogen (Note 2) is maintained in the vessel throughout the reaction with a nitrogen line connected both to a pressure relief valve and to a hypodermic needle which is inserted through the rubber septum. To the cold reaction vessel is added from a hypodermic syringe a solution of 2.53 g. (3.60 ml. or 25.0 mmoles) of pure diisopropylamine (Note 3) in 25 ml. of absolute ether (Note 4). An ethereal solution containing 25 mmoles of methyllithium (Note 5) is added from a hypodermic syringe dropwise and with stirring. During this addition a vigorous evolution of methane is observed. After the solution of lithium diisopropylamide has been stirred at 0° for 5–10 minutes a negative Gilman color test[2] for methyllithium is obtained. A solution of 3.13 g. (25 mmoles) of ethylidenecyclohexylamine in 20 ml. of absolute ether (Note 4) is added from a hypodermic syringe, dropwise and with stirring, to the cold (0°) solution of lithium diisopropylamide, and the resulting solution is stirred for 10 minutes (Note 6). This solution is then cooled to −70° with a dry ice-methanol bath, and a solution of 4.55 g. (25 mmoles) of benzophenone in 25 ml. of absolute ether is added to the cold (−70°) reaction vessel with a hypodermic syringe. The resulting solution is allowed to warm to room temperature and stand for 24 hours during which time a white solid separates. The reaction mixture is cooled to 0° in an ice bath, treated with approximately 50 ml. of water, and then stirred at 0° for 30 minutes. The cold mixture is filtered with suction to remove the white crystalline product, and the organic phase from the filtrate is separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The combined residues from the filtration and concentration of the organic phase of the filtrate are recrystallized from hexane to separate 6.80–7.06 g. (89–92%) of 3-hydroxy-3,3-diphenylpropylidenecyclohexylamine as white needles, m.p. 127–128° (Note 7).

C. *β-Phenylcinnamaldehyde.* A mixture of 1.54 g. (5.02 mmoles) of 3-hydroxy-3,3-diphenylpropylidenecyclohexylamine and 10 g. (0.11 mole) of oxalic acid is subjected to steam distillation. The steam distillation is continued until a clear distillate is obtained; this requires about 2 hours. The steam distillate is extracted with two 25-ml. portions of ether and the combined ethereal extracts are dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residual crude product (approximately 1.0 g., m.p. 42–44°) is recrystallized from pentane to separate 0.80–0.88 g. (78–85%) of β-phenylcinnamaldehyde as pale yellow needles, m.p. 46–47° (Note 8).

2. Notes

1. The amine (m.p. −21°) should be cooled with stirring until it just begins to freeze. At this point the temperature of the external cooling bath should be maintained at −20° by the periodic addition of pieces of dry ice.

2. One suitable arrangement for the purification of nitrogen is described by H. Metzger and E. Müller in Houben-Weyl's "Methoden der organischen Chemie," Vol. 1, Part 2, 4th ed., E. Müller, ed., Georg Thieme Verlag, Stuttgart, Germany, 1959, p. 327. The checkers used a prepurified grade of nitrogen without further purification.

3. The diisopropylamine (b.p. 83–84°, available from Fluka AG or from Eastman Organic Chemicals) is purified by refluxing it over either sodium wire or sodium hydride for approximately 30 minutes and then distilling the amine into a dry receiver under a nitrogen atmosphere. Because of the relatively low boiling point of the amine, the dispersion of sodium hydride in mineral oil available from Metal Hydrides, Inc., Beverly, Massachusetts, can be used directly in this purification without prior removal of the mineral oil.

4. The submitters purified diethyl ether by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted when benzophenone was added and then distilling the ether into a dry receiver under a nitrogen atmosphere. The checkers further purified an absolute grade of ether obtained from Mallinckrodt Chemical Works by distilling it from lithium aluminum hydride under a nitrogen atmosphere.

5. An ethereal solution of methyllithium may be prepared in the following manner. A dry 1-l. three-necked flask is fitted with a magnetic stirrer, a gas inlet tube, and a dry ice reflux condenser. In the flask are placed 800 ml. of absolute ether (Note 4) and 16 g. (2.3 g. atoms) of pieces of lithium wire. Over a period of 4–5 hours, 100 g. (1.05 moles) of methyl bromide is allowed to distill into the reaction flask with continuous stirring. The resulting mixture is stirred for an additional hour and then is allowed to stand overnight under a nitrogen atmosphere to permit the insoluble particles to settle. The supernatant liquid is transferred under a nitrogen atmosphere to a dry storage buret or some other dry vessel capped with a rubber septum. Alternatively, an ethereal solution of methyllithium may be purchased from Foote Mineral Co., Exton, Pennsylvania.

Aliquots of the methyllithium solution should be removed from the storage buret or storage vessel for standardization.The checkers employed the titration procedure of Watson and

Eastham[3,4] with either 2,2′-dipyridyl or *o*-phenanthroline as an indicator for standardizing the methyllithium solution.

6. When an aliquot of this solution is subjected to a Gilman color test,[2] a wine-red color is obtained.

7. The product has infrared absorption ($CHCl_3$ solution) at 3250 (broad, associated OH) and 1665 cm.$^{-1}$ (C═N) with n.m.r. peaks ($CDCl_3$ solution) at δ 7.78 (1 H triplet, J = 4 Hz., CH═N), 7.0–7.7 (10 H multiplet, aryl CH), 3.12 (2 H doublet, J = 4 Hz., α-CH_2), and 1.0–3.0 (11 H multiplet, aliphatic CH).

8. The product has infrared absorption (CCl_4 solution) at 2720, 2745, and 2840 cm.$^{-1}$ (aldehyde CH) and at 1675 cm.$^{-1}$ (conjugated C═O) with ultraviolet maxima (95% ethanol solution) at 224 mμ (ϵ 13,500) and 300 mμ (ϵ 16,500) and n.m.r. peaks (CCl_4 solution) at δ 9.40 (1 H doublet, J = 8 Hz., aldehyde CH), 7.1–7.5 (10 H multiplet, aryl CH), and 6.22 (1 H doublet, J = 8 Hz., vinyl CH).

3. Discussion

Until recently it has not been possible to control the aldol condensation[5] so that the enolate anion derived from an aldehyde can be condensed with a carbonyl group of a ketone because of the rapidity of the self-condensation of the aldehyde. This problem can be circumvented if the aldehyde is first converted to the corresponding azomethine derivative. The anion derived from this "protected" aldehyde can be added to another carbonyl group to give an easily crystallized β-hydroxy imine adduct. Subsequent dehydration and concurrent removal of the imino protecting group yields an α,β-unsaturated aldehyde. This overall procedure constitutes a new procedure for effecting an aldol condensation which utilizes an organometallic intermediate.[6–8] This procedure can be applied to a variety of aldehydes or ketones as carbonyl components. By use of the reaction conditions illustrated in this preparation other carbonyl compounds with acidic alpha C—H bonds such as acetone or β-ionone can also be used because the deprotonation of the carbonyl compound by the metalated Schiff base is largely suppressed. This directed aldol condensation procedure is useful for the preparation of naturally occurring α,β-unsaturated carbonyl compounds or for the preparation of intermediates useful in the syntheses of these substances.[9] The method can also be applied to the synthesis of α,β-unsaturated ketones if a ketimine is used as the azomethine component in the condensation.[9] Although the condensation is also successful with acetaldimine derivatives which contain one α-alkyl substituent, only very poor yields of condensation products are obtained when two α-alkyl substituents are present.[8,9] This limitation is possibly the result of a retarded rate of proton abstraction from the imine as a result of the steric hindrance offered by the α-alkyl substituents.[10]

Although the reaction of aldehydes with β-carbonylmethylene phosphoranes constitutes a good synthetic route to α,β-unsaturated carbonyl compounds,[11–14] this procedure is normally not applicable to ketones. This limitation has recently been overcome by the reaction of ketones with the cyclohexylimine derivative of β-carbonylmethylenephosphonates.[15]

With the aid of the directed aldol condensation procedure, 3-hydroxy-3,3-diphenylpropylidenecyclohexylamine has been prepared for the first time. Previous methods employed for the synthesis of β-phenylcinnamaldehyde include the application of the Sommelet reaction to 3,3-diphenylallyl bromide with isolation of the aldehyde as its semicarbazone,[16] the reaction of β,β-diphenylvinylmagnesium bromide with N-methylformanilide followed by hydrolysis,[17] and the reaction of this same Grignard reagent with ethyl orthoformate followed by hydrolysis of the resulting acetal.[18] This unsaturated aldehyde has also been prepared by the formylation of 1,1-diphenylethylene with N-methylformanilide and phosphorus oxychloride,[19] by the oxidation of β-phenylcinnamyl alcohol with manganese dioxide,[20] and by the rearrangement of 1,1-diphenyl-2-propyn-1-ol in an ethylene glycol solution containing boron trifluoride and mercury(II) oxide followed by hydrolysis of the intermediate acetal.[21]

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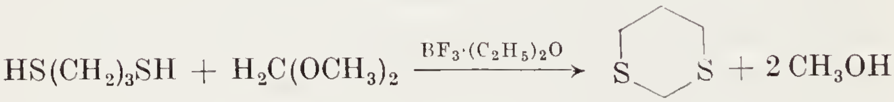
1,3-DITHIANE

(*m*-Dithiane)



Submitted by E. J. Corey and D. Seebach[1]
Checked by J. C. Reilly and W. D. Emmons

1. Procedure

In a 1-l. three-necked round-bottomed flask with ground-glass fittings is placed a mixture of 36 ml. of boron trifluoride etherate, 72 ml. of glacial acetic acid, and 120 ml. of chloroform (Note 1). The flask is equipped with a spiral reflux condenser, an efficient mechanical stirrer, and a dropping funnel (Note 2). The chloroform solution in the flask is heated and maintained at reflux with vigorous stirring, and a solution of 30 ml. of 1,3-propanedithiol (0.30 mole) and 29 ml. of methylal (0.33 mole) in 450 ml. of chloroform (Note 1) is added at a constant rate over 8 hours. The mixture is allowed to cool to room temperature, washed successively with four 80-ml. portions of water, twice with 120 ml. of 10% aqueous potassium hydroxide, and twice with 80-ml. portions of water. The chloroform solution thus obtained is dried over potassium carbonate and concentrated in a 500-ml. round-bottomed flask under reduced pressure using a rotating flask evaporator (Note 3). The residue, which crystallizes on cooling to room temperature, is dissolved in 60 ml. of methanol by heating to the boiling point. The hot solution is filtered rapidly through a prewarmed funnel, allowed to cool slowly to room temperature, and then kept overnight at −20°. The colorless crystals are collected by filtration through a prechilled Buchner funnel, washed with cold methanol (−20°), and dried under reduced pressure (Notes 3 and 4). The yield of dry product, m.p. 53–54°, is 28–29 g. Solvent is removed from the mother liquor, and the residue is recrystallized as described to furnish an additional 1.5–2.0 g.; the total yield of recrystallized 1,3-dithiane is 29.5–31.0 g. (82–86% based on propane-1,3-dithiol). A purer sample (Note 5) can be prepared by subsequent sublimation of the recrystallized product at 0.1–0.5 mm. (45–48° bath temp.) (Note 6). The yield of pure product is 28–30 g. (78–84%), m.p. 53–54°. The residue from the sublimation is a brown syrup weighing less than 1 g.

2. Notes

1. The following components were used as supplied: boron trifluoride etherate, Eastman white label; chloroform and methylal, Fischer reagent; glacial acetic acid, du Pont reagent; 1,3-propanedithiol, Aldrich Chemical Co. The submitters have scaled up this preparation by a factor of 5 without difficulty.

2. Neither the boron trifluoride etherate nor the acetic acid should be added through the dropping funnel, since the presence of even small amounts of acid in the funnel would catalyze undesired condensation of the reagents to be added later. Furthermore the reagents added from the dropping funnel should fall directly into the boiling liquid.

3. Owing to the volatility of 1,3-dithiane, the pressure should be above 30 mm., and the operation should not be prolonged.

4. The crude product can also be distilled; b.p. 95° at 20 mm.

5. This additional purification is recommended if the 1,3-dithiane is to be used in organometallic reactions.[2]

6. Using a sublimator large enough to contain all the recrystallized product obtained, the sublimation can be completed in *ca.* 2 hours at 0.1 mm.

3. Discussion

Although many workers have reported studies with 1,3-dithiane,[3–7] no satisfactory description of its preparation has been published. Generally, 1,3-propanedithiol and formaldehyde[3,5,7] have been used as components; in one instance, 1,3-dibromopropane was treated with sodium thiosulfate to form a precursor of the dithiol which was used as such with formalin.[4] The formation of linear condensation products is a serious side reaction under such conditions.

The procedure given here is a simple and efficient method for producing 1,3-dithiane, a valuable intermediate in the synthesis *via* lithio derivatives of a wide variety of compounds, including aldehydes, ketones, α-hydroxyketones, 1,2-diketones, and α-keto acid derivatives.[2]

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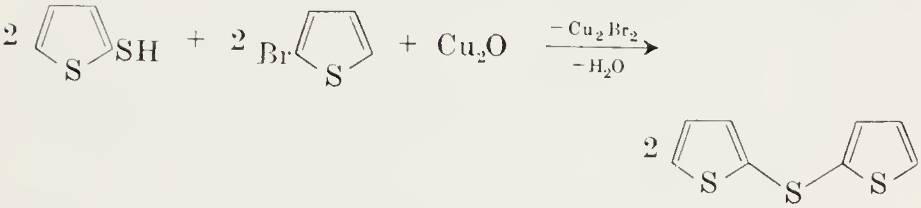
2,2′-DITHIENYL SULFIDE

(2,2′-Thiodithiophene)



Submitted by E. JONES and I. M. MOODIE[1]
Checked by JERRY G. KOHLHOFF, WAYLAND E. NOLAND,
and WILLIAM E. PARHAM

1. Procedure

In a three necked 250-ml. flask fitted with a reflux condenser stirrer and a thermometer pocket with a nitrogen inlet are placed 100 ml. of N,N-dimethylformamide, 5.6 g. (0.10 mole) of potassium hydroxide (Note 1), and 7.15 g. (0.050 mole) of freshly precipitated cuprous oxide[2] (Note 2). 2-Bromothiophene (16.4 g., 0.10 mole) (Note 3) is then added and the apparatus flushed with nitrogen (Note 4). 2-Thiophenethiol[3,4] (11.6 g., 0.10 mole) is then added slowly through the condenser; an exothermic reaction sets in and the temperature may rise to 50–60°. The flask is heated in an oil bath at 130–140° for 16 hours (Note 5). The mixture is cooled to room temperature and the contents of the flask are poured into 100 ml. of 6 *N* hydrochloric acid in ice and the mixture is stirred vigorously for 2 hours (Note 6). The oily black paste obtained is removed by filtration and thoroughly extracted in a Soxhlet extractor with benzene until a colorless extract is obtained. The filtrate is also extracted with two 100-ml. portions of benzene. These extracts are combined, washed with water until neutral, and finally dried over anhydrous sodium sulfate. Removal of the benzene solvent gives a yellow-colored oil which, on vacuum distillation, yields 2,2′-dithienylsulfide as a pale yellow oil, b.p. 75–78° (0.06 mm.) n^{25}_{D} 1.6643. The yield is 11.5–12.5 g. (58–63%).

2. Notes

1. The presence of an equivalent of potassium or sodium hydroxide is necessary to promote the substitution reaction of the 2-bromothiophene with cuprous oxide.

2. The freshly precipitated cuprous oxide was dried at 110° before use. Commercial grades of cuprous oxide were found to give lower yields (*ca.* 35–40%) of the desired sulfide. The checkers dried cuprous oxide in a vacuum oven at 100° for 6 hours.

3. 2-Bromothiophene was supplied by Columbia Organic Chemicals, Inc. 2-Chloro- or 2-iodothiophenes may be used; however, the former gives poorer yields of the sulfide.

4. Nitrogen is passed through the system to provide an inert atmosphere, thereby preventing possible oxidation of the 2-thiophenethiol to the corresponding disulfide.

5. Reaction is sluggish at temperatures below 130°.

6. Vigorous stirring helps to break up the thick sludge formed on addition of the reaction mixture to the acid and also serves to remove soluble inorganic salts.

3. Discussion

The submitters have also prepared 2,2′-dithienyl sulfide in 34% yield by condensation of 2-thiophenethiol with 2-bromothiophene in the presence of cuprous oxide in a quinoline-pyridine mixture.[5] Challenger and Harrison[6] have obtained 2,2′-dithienyl sulfide in 50–55% yield by treatment of 2-thienylmagnesium bromide with excess sulfur. This sulfide may also be obtained in 20% yield by condensation of thiophene with sulfur monochloride, followed by pyrolysis of the resultant disulfide.[7]

This synthetic process offers a route to the preparation of the isomeric dithienyl sulfides[8] (2,3- and 3,3-) which cannot be prepared readily by any of the standard literature methods. Thus condensation of 2-thiophenethiol with 3-bromothiophene or 3-thiophenethiol with 2-bromothiophene gives 2,3′-dithienyl sulfide in 63.0 and 73.5% yields, respectively. Similarly, 3,3′-dithienyl sulfide is obtained in 48% yield. The method has also been extended to the synthesis of the isomeric *bis*-(thienylthio)thiophenes in 40–50% yield.[5]

This method may also be used for the preparation in high yields of other aromatic sulfides.[9]

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ETHYL 1-NAPHTHYLACETATE

(1-Naphthaleneacetic acid, ethyl ester)

$$1\text{-}C_{10}H_7COCl + CH_2N_2 + (C_2H_5)_3N \rightarrow 1\text{-}C_{10}H_7COCHN_2 + (C_2H_5)_3\overset{+}{N}H\,Cl^-$$

$$1\text{-}C_{10}H_7COCHN_2 + C_2H_5OH \xrightarrow[(C_2H_5)_3N]{C_6H_5CO_2Ag} 1\text{-}C_{10}H_7CH_2CO_2C_2H_5 + N_2$$

Submitted by Ving Lee and Melvin S. Newman[1]
Checked by Gordon F. Hambly and Peter Yates

1. Procedure

Caution! Diazomethane is hazardous. Follow the directions for its safe handling given in earlier volumes.[2,3] *The intermediate,* 1-(*diazoacetyl*)*naphthalene, is a very strong skin irritant.*

A. 1-(*Diazoacetyl*)*naphthalene.* A solution of 30.5 g. (0.160 mole) of 1-naphthoyl chloride (Notes 1 and 2) in 50 ml. of dry ether (Note 3) is added during 30 minutes to a magnetically stirred, ice-cooled solution of 6.72 g. (0.160 mole) of diazomethane[4] (Note 4) and 16.1 g. (0.160 mole) of dry triethylamine (Note 5) in 900 ml. of dry ether. The mixture is stirred for 3 hours in the cold, and the triethylamine hydrochloride is removed by filtration and washed twice with 30–50 ml. portions of dry ether (Note 6). The ether is removed from the combined filtrate and washings on a rotary evaporator under reduced pressure. The yellow solid residue is dissolved in 75 ml. of dry ether, and the solution is cooled by a dry ice-acetone mixture. The solid deposited is collected by filtration on a glass fritted-disk funnel, and the adhering ether is removed under reduced pressure as the temperature is allowed to reach room temperature. There is obtained 26.6–28.8 g. (85–92%) of yellow 1-(diazoacetyl)naphthalene, m.p. 52–53° (Notes 7 and 8).

B. *Ethyl 1-naphthylacetate.* A solution of 15.7 g. (0.080 mole) of 1-(diazoacetyl)naphthalene in 50 ml. of absolute ethanol is placed in a 100-ml. two-necked flask equipped with a Teflon-coated magnetic stirring bar, a serum stopper cap, and a reflux condenser connected at the top to a gas-collecting device. The solution is heated to reflux, and 1 ml. of a freshly prepared catalyst solution made by dissolving 1 g. of silver benzoate (Note 9) in 10 ml. of triethylamine is added by injection through the serum cap. Evolution of nitrogen occurs and the mixture turns black. Addition of a second milliliter of catalyst solution is made when the evolution of nitrogen almost stops. This procedure is continued until further additions cause no further evolution of nitrogen (Note 10). The reaction mixture is refluxed for 1 hour, cooled, and filtered. The solvents are removed from the filtrate on a rotary evaporator under reduced pressure. The residue is taken up in 75 ml. of ether, and the solution is washed twice in turn with aqueous 10% sodium carbonate, water, and saturated brine. Each aqueous extract is extracted with ether, and the combined ethereal extracts and solution are dried by filtration through anhydrous magnesium sulfate. After removal of the ether, distillation affords 14.4–15.8 g. (84–92%) of colorless ethyl 1-naphthylacetate, b.p. 100–105° (0.1–0.2 mm.) (Note 11).

2. Notes

1. The submitters prepared pure 1-naphthoyl chloride, b.p. 95–96° (0.2 mm.), from pure 1-naphthoic acid in 95% yield by treatment with thionyl chloride or phosphorus pentachloride. The pure 1-naphthoic acid used was prepared by carbonation of

1-naphthylmagnesium bromide. As commercial 1-bromonaphthalene is impure, fractionation through a 17 × 600 mm. column is needed to obtain pure 1-bromonaphthalene, b.p. 105–108° (0.1–0.2 mm.), as indicated by vapor phase chromatography.

2. The checkers prepared 1-naphthoyl chloride by treatment of 1-naphthoic acid, m.p. 157–161°, obtained from Aldrich Chemical Co., with phosphorus pentachloride.

3. All dry ether used was freshly distilled from ethylmagnesium bromide.

4. Solutions of diazomethane in ether were titrated with benzoic acid.

5. Triethylamine was dried by storage over anhydrous barium oxide.

6. About 90% of the theoretical yield of triethylamine hydrochloride is obtained.

7. This compound is a severe skin irritant, hence great care should be exercised to avoid any contact. For best yields in the rearrangement step this crystallization is recommended, since the yield of ethyl 1-naphthylacetate is reduced by about 20% if the crude product is used in the rearrangement. A sample of crystallized 1-(diazoacetyl)naphthalene, m.p. 52–53°, that had been stored in a screw-top bottle in a refrigerator for about 2 weeks afforded the same yield of ethyl 1-naphthylacetate as a freshly prepared sample.

8. The checkers obtained 26.1–26.5 g. (83–84.5%) of 1-(diazoacetyl)naphthalene, m.p. 47–49.5°, when 1-naphthoyl chloride prepared from commercial 1-naphthoic acid was used (cf. Notes 1 and 2). Recrystallization from hexane gave 24.6 g. (78%) of 1-(diazoacetyl)naphthalene, m.p. 49.5–52°, that was used in Part B.

9. The silver benzoate was made by reaction of silver nitrate with sodium benzoate in water. The submitters dried the silver benzoate and recrystallized it from N-methylpyrrolidone or dimethylformamide. The checkers dried it in an oven at 130° for 1 hour immediately before use, but did not recrystallize it. Any precipitate present after dissolving the silver benzoate in triethylamine is removed by filtration or centrifugation.

10. Usually 3–4 additions are required. The total time of reaction should not be more than 45 minutes. The checkers added the catalyst solution in 0.5-ml. portions; nitrogen evolution was initially very vigorous, and only four such additions were required.

11. When propyl alcohol is used instead of ethyl alcohol, comparable results are obtained. Propyl 1-naphthylacetate has b.p. 115–118° (0.1–0.2 mm.).

3. Discussion

Ethyl 1-naphthylacetate has been prepared by ethanolysis of 1-naphthylacetonitrile under acidic conditions[5] and by the Arndt-Eistert reaction of 1-(diazoacetyl)naphthalene with ethanol and silver oxide.[6]

The method described here represents a modified Arndt-Eistert reaction as developed by Newman and Beal.[7] This modification gives results that are more reproducible than those of the original Arndt-Eistert reaction and, in general, allows the rearrangement to be carried out successfully on larger-scale runs. The use of triethylamine in the formation of diazo ketones makes possible the use of only one equivalent of diazomethane.[8]

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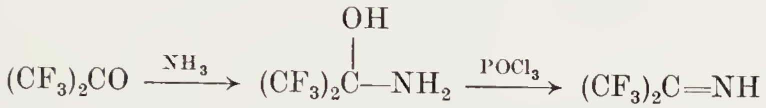
HEXAFLUOROACETONE IMINE

(2-Propanone, hexafluoro-; imine)



$$(CF_3)_2CO \xrightarrow{NH_3} (CF_3)_2\overset{\displaystyle OH}{\overset{|}{C}}—NH_2 \xrightarrow{POCl_3} (CF_3)_2C{=}NH$$

Submitted by W. J. Middleton and H. D. Carlson[1]
Checked by L. Scerbo and W. D. Emmons

1. Procedure

Caution! This procedure should be conducted in a good hood to avoid exposure to ammonia and hexafluoroacetone.

A 3-l. four-necked round-bottomed flask is equipped with a thermometer (−50° to 150°), a dry ice-cooled reflux condenser (protected from the atmosphere through a T-tube that is also connected to a nitrogen source and a Nujol bubbler), and a gas inlet tube above the liquid level. The flask and condenser are heated in an air oven at 125° for several hours and flamed out under nitrogen with a Bunsen burner after being assembled. Into the flask is poured 1.2 l. of pyridine which has previously stood over KOH pellets. As a nitrogen atmosphere is maintained in the system, the pyridine is cooled to −40° and 462 g. (2.8 moles) of hexafluoroacetone (b.p. −28°) is added from a cylinder through the gas inlet tube in about 30 minutes (Notes 1, 2, and 3). A 58.3-ml. charge (47.6 g., 2.8 moles) of liquid ammonia, previously distilled into a cold trap and measured at −78°, is then distilled into the pyridine solution over a period of 1 hour (Note 4). During this addition the bath is held at −45° to −40° to keep the solution at −25° to −30°.

As soon as the ammonia has been added, the gas inlet tube is replaced with a 250-ml. pressure-equalized dropping funnel and the reaction mixture is heated by means of a heating mantle to 40° in about 30 minutes or as quickly as possible (Note 5). The solid carbon dioxide-cooled condenser is then replaced with a 24-in. water-cooled bulb condenser with Tygon tubing joining the top of the condenser to a 300-ml. cold trap protected from the atmosphere with a calcium chloride drying tube and cooled in a bath maintained at −30°. The condenser is cooled with 18–20° water. The heating mantle is turned off, and the dropping funnel is charged with 235 ml. (394 g., 2.6 moles) of phosphorus oxychloride, which is added dropwise at a rate to maintain a gentle reflux. The imine (b.p. 16°) collects in the cold trap. When addition is complete, the reaction mixture is heated to 100° in about 20 minutes and maintained at this temperature for 30 minutes. There is collected in the cold trap 320–360 g. of crude liquid product (Note 6), which is distilled through a Podbielniak still with a reflux head temperature of about 0° (Note 7). The yield of purified imine, b.p. 15.5–17°, is 254–291 g. (55–65%) (Note 8). It can be stored indefinitely in a stainless steel cylinder.

2. Notes

1. Hexafluoroacetone may be obtained from E. I. du Pont de Nemours and Company, Inc., or Allied Chemical Corporation.

2. If it is inconvenient to add the hexafluoroacetone directly from a cylinder, it may first be condensed in a calibrated trap containing a boiling chip and cooled in a solid carbon dioxide-acetone bath. When cooled to −78°, 462 g. of liquid hexafluoroacetone is about 280 ml. The hexafluoroacetone can be added to the reaction mixture by allowing it to boil slowly from the trap.

3. The bath is maintained at −40° and the pyridine solution is maintained below −20°. Acetone to which pieces of dry ice are added periodically to adjust the temperature is a convenient cooling bath.

4. The ammonia can be prevented from bumping by means of a magnetic stirrer in the trap. Heat for the distillation can be obtained from the air of the laboratory and by occasionally flushing the outside wall of the trap with room-temperature acetone.

5. Prolonged heating decreases the yield.

6. For storage until Podbielniak distillation can be carried out, the product can be drained into an evacuated stainless steel cylinder of 500 ml. capacity.

7. The checkers used a 60-cm. vacuum-jacketed column packed with glass helices with satisfactory results.

8. This preparation has been run in the submitters' laboratory at four times this scale with yields as high as 67%.

3. Discussion

Hexafluoroacetone imine has been prepared by the reaction of hexafluoroacetone with triphenylphosphine imine,[2] by the pyrolysis of N-phenyl-2,2-diaminohexafluoropropane,[2,3] by the reaction of hexafluorothioacetone with hydrazoic acid,[4] and by the reaction of ammonia and phosphorus oxychloride with hexafluoroacetone.[4,5] The latter method, which is described here, is the most convenient for it does not require preparation of several intermediates or use of pressure equipment. This method has also been used to prepare the imines of other fluoroketones, including the imines of chloropentafluoroacetone, dichlorotetrafluoroacetone, and perfluorodiethyl ketone.[5] Substitution of methylamine for ammonia in this procedure gives the N-methyl imine.[5]

1. Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware.
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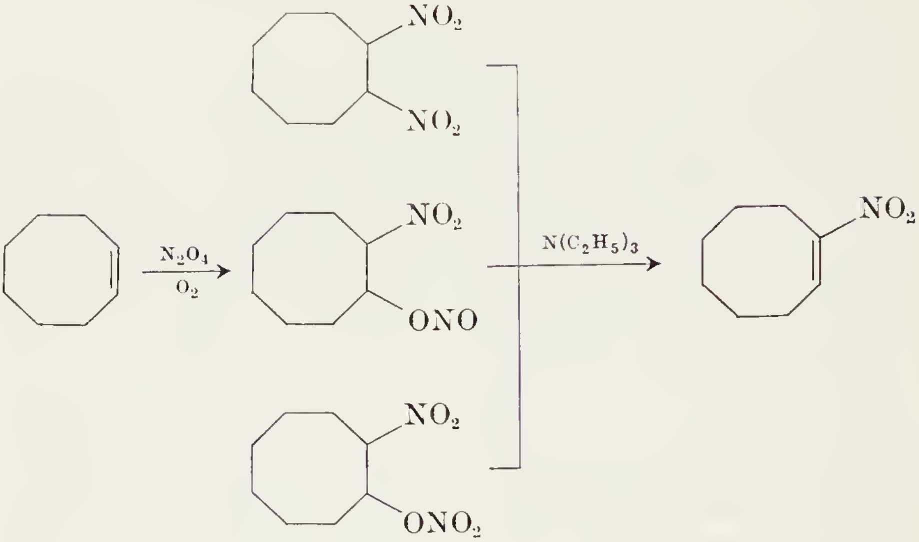
1-NITROCYCLOOCTENE

(Cyclooctene, 1-nitro-)



Submitted by WOLFGANG K. SEIFERT[1]
Checked by E. LEWARS, P. H. MCCABE, and PETER YATES

1. Procedure

Caution! Dinitrogen tetroxide is very toxic (Note 1), and nitro nitrites are unstable. The reaction must be carried out in a well-ventilated hood with an adequate shield.

Sodium-dried ether (150 ml.) is placed in a 1-l. four-necked flask equipped with a fritted gas inlet extending to its bottom, a sealed mechanical stirrer (Note 2), a 100-ml. pressure-equalizing dropping funnel, a thermometer, and a dry ice condenser protected with a phosphorus pentoxide drying tube. Cyclooctene (44.4 g., 53.5 ml., 0.40 mole) (Note 3) is placed in the dropping funnel, and the system is swept with dry oxygen. Dinitrogen tetroxide (39.3 g., 27.1 ml. at −9°, 0.43 mole) (Note 4) is condensed (Note 5) in a graduated calibrated trap that is protected with a phosphorus pentoxide drying tube and has been swept with dry oxygen.

The flask is cooled to −10°, and the dinitrogen tetroxide is distilled with a warm water bath from the trap into the ether with slow stirring; the transfer is aided by a minimum flow of dry oxygen. The solution is allowed to warm to 0–5°, and the oxygen flow rate is increased to 10 ml. per minute (Note 6). The cyclooctene is dropped into the dinitrogen tetroxide solution over a 30-minute period with vigorous stirring; the reaction is exothermic, and the temperature is kept at 9–12° by cooling with a dry ice-methanol bath at $-20°$. The dropping funnel is rinsed with 25 ml. of ether, and the yellow solution (Note 7) is stirred for an additional 30 minutes at 10° with continued oxygen flow. Triethylamine (121 g., 1.2 moles) (Note 8) is added over a period of 12 minutes with stirring; the temperature of the reaction mixture is kept at 4–12° by maintaining the bath at $-4°$ (Note 9). The mixture is kept at room temperature for an additional 30 minutes, diluted with 150 ml. of ether, and cooled to 0–5°. The excess triethylamine is neutralized with an ice-cold solution of 72 g. of acetic acid in 200 ml. of water with stirring. The reaction mixture is transferred to a 2-l. separatory funnel and extracted with three 400-ml. portions of ether. The combined ethereal extracts are washed with two 200-ml. portions of water, three 150-ml. portions of saturated aqueous sodium bicarbonate, and again with water (Note 10).

Most of the ether is removed under reduced pressure at room temperature with a rotary evaporator. The water that separates is removed with the aid of a small separatory funnel, and the remaining ether, traces of water, and cyclooctane (Note 11) are distilled at room temperature under a pressure of 10 mm. during 3 hours; 59–61 g. of crude 1-nitrocyclooctene remains as a yellow oil (Notes 12 and 13). Purification is effected by chromatography on silica gel (Note 14) with successive elution with *n*-hexane and benzene to give 39–40 g. (63–64%) of 1-nitrocyclooctene (Note 15). Distillation (Note 16) gave an analytically pure sample, b.p. 60° (0.2 mm.), $n^{20}\text{D}$ 1.5116 (Note 17).

2. Notes

1. Concentrations of dinitrogen tetroxide of 100–150 p.p.m. are dangerous for exposures of 30–60 minutes, and concentrations of 200–700 p.p.m. may be fatal after even very short exposures.

2. The checkers found that magnetic stirring could be used in place of mechanical stirring.

3. Cyclooctene (95% pure) from Columbia Carbon Co., a division of Cities Service, was used without further purification.

4. A slight excess of dinitrogen tetroxide over olefin is necessary for maximum yields.

5. For good yields all reagents must be absolutely dry. For condensation of dry dinitrogen tetroxide free of dinitrogen trioxide, streams of dry oxygen (run through a flow meter, a calcium chloride tube, and concentrated sulfuric acid) and dinitrogen tetroxide (99.5% pure from the Matheson Company), are combined and run slowly through a phosphorus pentoxide tube before condensation. The freezing point of dinitrogen tetroxide is −9.3°, and a convenient cooling bath for condensation is dry ice-methanol at −8° to −10°.

6. The use of oxygen in this reaction prevents formation of undesirable by-products, *e.g.*, nitro nitroso compounds.[2] For the preparation of 1-nitro-1-octadecene the optimum mole ratio of olefin to oxygen was found[3] to be 1/50 to 1/150, compared with 1/30 in this procedure.

7. Nitro nitrites are unstable, and it is safe practice to keep them in solution until they are converted to nitro alcohols[2] or nitro olefins.[3]

8. Commercial triethylamine (Eastman Kodak Co.) was used without further purification. Stoichiometric amounts of triethylamine based on olefin produced poor yields of nitro olefins owing to the slow rate of elimination of the nitro nitrite compounds.[3] A twofold molar ratio of triethylamine to olefin was sufficient to produce 1-nitro-1-octadecene from 1-nitro-2-octadecyl nitrite in 92% yield.[3] The same excess applied to the crude reaction product from cyclooctene and dinitrogen tetroxide resulted in only an 80% yield of 1-nitrocyclooctene.

9. At the end of the elimination reaction, which is exothermic, the color turns brown with simultaneous precipitation of the triethylammonium salts.

10. The checkers washed the ethereal extracts with saturated brine and dried them over anhydrous magnesium sulfate before removal of ether.

11. Cyclooctane is the major impurity in the starting material.

12. The submitter estimated the crude product to be 95% pure by infrared spectroscopy: $\varepsilon_{6.59\mu}/\varepsilon_{3.40\mu} = 3.00$ (CCl_4: matched 0.1-mm. cells; analytical absorbances, 0.2–0.7).

13. For further reactions involving reduction,[4] the crude product can be used.

14. The silica gel column was 14 × 2.5 in. I.D.; a shorter column may suffice.

15. The checkers found for this product: n^{26}D 1.5106; δ $CDCl_3$ 1.6 (m, 8 H), 2.3 (m, 2 H), 2.7 (m, 2 H), and 7.24 (t, $J = 9$ Hz., 1 H).

16. It is safe practice to remove the peroxide that may be formed in this free radical reaction by chromatography before distillation. The submitter distilled an aliquot (12.7 g.) of the hexane eluate to give 9.9 g. of product, $\varepsilon_{6.59\mu}/\varepsilon_{3.40\mu} = 3.12$ (Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.84; H, 8.27; N, 8.80).

17. Slow decomposition with simultaneous precipitation of a solid occurred on standing for several weeks at 23°. Immediate analysis and use of the product are advised.

3. Discussion

The major advantage of the present method, which is the only method reported[3] for the preparation of 1-nitrocyclooctene, is the convenience of converting an olefin to a 1-nitro olefin in good yield without isolation of any intermediate. The submitter has also used this method[3] successfully for the preparation of 1-nitro-1-octadecene from 1-octadecene.

In the past the products from the addition of dinitrogen tetroxide to olefins have been hydrolyzed and then converted to 1-nitro olefins by various methods, *e.g.*, acetylation of the isolated nitro alcohol and elimination of acetic acid with potassium carbonate,[5,6] dehydration of the nitro alcohol with phthalic anhydride[7] or potassium hydrogen sulfate,[8] and base-catalyzed elimination of nitrous and nitric acid from dinitro compounds and nitro nitrates, respectively.[2] Besides representing longer syntheses, these routes require separation of the nitro alcohol from the dinitro compound and, since these substances occur in approximately equal amounts, 50% of the yield is lost in the first step. Furthermore, in the case of the higher 1-olefins, this separation is difficult[9,10] and tedious.[3] 1-Nitro 1-olefins have been employed in the preparation of saturated nitro compounds and oximes.[4]

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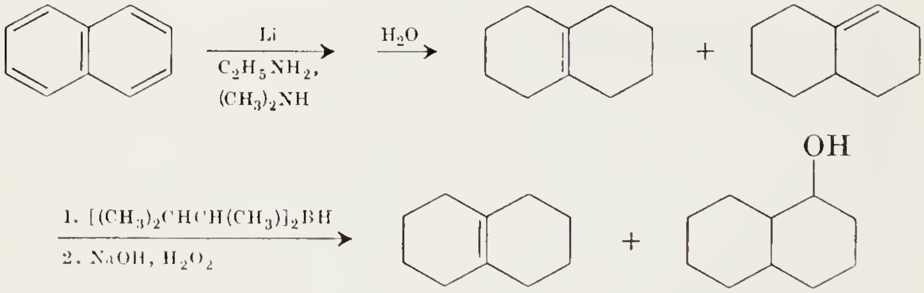
$\Delta^{9,10}$-OCTALIN

(Naphthalene, 1,2,3,4,5,6,7,8-octahydro-)



Submitted by Edwin M. Kaiser[1] and Robert A. Benkeser[2]
Checked by Frederick J. Sauter and Herbert O. House

1. Procedure

A. $\Delta^{9,10}$- *and* $\Delta^{1,9}$-*Octalin. Caution! This preparation should be performed in a hood to avoid exposure to amine vapors.* Naphthalene (25.6 g. or 0.20 mole, Note 1) is dissolved in a mixture of 250 ml. of anhydrous ethylamine and 250 ml. of anhydrous dimethylamine (Note 2) in a 1-l. three-necked flask fitted with a mechanical stirrer (Note 3) and a dry ice condenser and cooled in an ice bath. To this solution is added rapidly (Note 4) and piecewise with stirring, 11.55 g. (1.66 g. atoms) of lithium metal wire cut into 0.5-cm. lengths (Note 5). After the addition is complete, the cooling bath is removed and the blue solution is stirred for 14 hours, additional dry ice being added to the condenser as required. The dry ice condenser is then replaced with a water condenser and the mixture is allowed to stand overnight during which time the volatile amine solvents evaporate (Note 6). The top of the condenser is protected with a drying tube packed with anhydrous calcium sulfate to maintain anhydrous conditions in the reaction vessel during the evaporation of solvent (Note 7). The reaction flask is then placed in an ice bath and the grayish-white residue is hydrolyzed by the *cautious* addition of 500 ml. of water dropwise with occasional stirring. After the resulting suspension has been filtered with suction, the residual solid is washed with four 25-ml. portions of ether. The ether layer is separated and the aqueous phase of the filtrate is extracted with four additional 25-ml. portions of ether. The combined ethereal solutions are dried over calcium sulfate and then concentrated with a rotary evaporator. The residual liquid is distilled under reduced pressure to separate 19–20 g. (70–74%) of the product, b.p. 72–77° (14 mm.), $n^{23}\text{D}$ 1.4978. Analysis of the product by gas chromatography (Note 8) shows the presence of 80–83% of $\Delta^{9,10}$-octalin and 17–20% of $\Delta^{1,9}$-octalin. This mixture should be either stored under a nitrogen atmosphere or immediately subjected to the subsequently described purification procedure (Note 9).

B. *Purification of $\Delta^{9,10}$-Octalin.* A 1-l. three-necked flask is equipped with a magnetic stirrer, a pressure-equalizing dropping funnel, and a reflux condenser fitted with a nitrogen inlet tube to maintain a nitrogen atmosphere in the reaction vessel throughout the portions of this preparation where anhydrous conditions are employed. A solution of 2.35 g. (0.062 mole) of sodium borohydride and 11.55 g. (0.164 mole) of 2-methyl-2-butene (Note 10) in 100 ml. of anhydrous tetrahydrofuran is added to the reaction flask, and then a solution of 11.75 g. (0.083 mole) of boron trifluoride etherate in 22 ml. of anhydrous tetrahydrofuran is added, dropwise and with stirring, over a 45-minute period. Although the initial rate of addition must be slow to maintain control over the exothermic reaction, the addition rate can be increased during the latter part of the reaction. To the resulting solution of bis-(3-methyl-2-butyl)-borane in tetrahydrofuran is added, dropwise and with stirring during 10 minutes, the mixture of $\Delta^{9,10}$- and $\Delta^{1,9}$-octalins (19–20 g. containing *ca.* 0.03 mole of $\Delta^{1,9}$-octalin) obtained in Part A. The reaction mixture is stirred at room temperature for 3.5 hours and treated with 50 ml. of water. After 35 ml. of aqueous 3 M sodium hydroxide has been added, dropwise and with stirring during 10 minutes, 35 ml. of aqueous 30% hydrogen peroxide is added dropwise over a 45-minute period with continuous stirring. The resulting mixture is heated to 45° (Note 11) with stirring for 5 hours and then allowed to cool to room temperature. The organic layer is separated, washed with four 30-ml. portions of water, and dried over calcium sulfate. After the organic solution has been tested with moist starch-iodide paper to ensure the absence of peroxides, the volatile solvents are removed with a rotary evaporator and the residual liquid is distilled under reduced pressure in an apparatus fitted with a capillary tube to admit nitrogen as an ebullator (Note 12). After 1–2 g. of forerun has been separated, 9–13 g. (33–48% based on the starting naphthalene) of $\Delta^{9,10}$-octalin is collected at 75–77° (14 mm.), $n^{20}\text{D}$ 1.4990. The product, which contains at least 99% of $\Delta^{9,10}$-octalin by gas chromatographic analysis (Note 8), should be stored under a nitrogen atmosphere (Note 9).

2. Notes

1. Naphthalene purchased from Eastman Organic Chemicals was used without purification.

2. The ethylamine (b.p. 16.6°) and dimethylamine (b.p. 7.4°) may be distilled into the reaction flask from cylinders. The checkers employed amines purchased from Eastman Organic

Chemicals in sealed ampules. After the ampules had been cooled to 0° in an ice bath, they were opened and the contents were added to flasks cooled in ice baths. Small portions (0.5–1.0 g.) of sodium metal were added to each of the cold amines, and then the cooling baths were removed and the amines allowed to distill from the sodium into the reaction flask.

3. Stirrers with Teflon paddles should not be used. Although the reaction proceeds satisfactorily, the Teflon parts are blackened (and presumably partially degraded) by the reaction solution.

4. The reaction is very exothermic during the initial addition of lithium metal. The use of an external ice bath for cooling reduces the number of times additional dry ice must be added to the condenser containing a dry ice-acetone mixture.

5. The lithium wire is supplied coated with a hydrocarbon grease to protect the metal. As 0.5-cm. pieces are cut from this wire with scissors, they should be dropped into a beaker of anhydrous hexane to dissolve the grease. The pieces of bare lithium wire are then removed with forceps, drained briefly by touching them to a dry towel, and weighed in a second beaker of anhydrous hexane. The pieces of metal are then removed from this second beaker with forceps as they are added to the reaction mixture.

6. If evaporation of the solvent is not complete, the remainder of the solvent can be removed by immersing the reaction flask in a bath of warm water.

7. If anhydrous conditions are not maintained, the product is contaminated with a tarry material.

8. A gas chromatography column packed with Apiezon L suspended on Chromosorb P was employed for this analysis. In a typical analysis at 140° the retention times were: $\Delta^{1,9}$-octalin, 46.2 minutes; $\Delta^{9,10}$-octalin, 49.2 minutes. The n.m.r. spectrum (CCl_4 solution at 60 mHz.) of this mixture exhibits a multiplet at δ 0.8–2.6 (aliphatic CH) with a weak, partially resolved multiplet at δ 5.25 (vinyl CH of $\Delta^{1,9}$-octalin).

9. The octalins usually react rapidly with oxygen of the air to form unidentified oxygenated products. The checkers found that, if the crude product is not protected from air oxidation,

the yield of $\Delta^{9,10}$-octalin isolated from the purification procedure is lowered substantially.

10. 2-Methyl-2-butene purchased either from Phillips Petroleum Company or Aldrich Chemical Co. was used without purification.

11. The checkers found use of a large oil bath a convenient method for heating the reaction mixture to 45°.

12. The mixture tends to foam badly during this distillation.

3. Discussion

Among the preparative routes to the octalin mixtures, the acid-catalyzed dehydration of 2-decalol[3] and the metal-amine reduction of naphthalene[4] appear most satisfactory. Apart from the purification method described in this preparation, pure $\Delta^{9,10}$-octalin has also been obtained by reaction of the octalin mixture with nitrosyl chloride. After separation of the adducts by fractional crystallization, the pure $\Delta^{9,10}$-octalin has been regenerated from its nitrosyl chloride adduct.[3,5]

Lithium dissolved in amines of low molecular weight constitutes a useful and convenient reagent for reducing aromatic hydrocarbons to monoolefins.[6] Although mixtures of isomeric olefins are usually obtained with primary amine solvents, the use of secondary amines as cosolvents dramatically increases the selectivity of these reductions so that the more thermodynamically stable olefin usually becomes the predominant product. Thus, in the reduction of naphthalene, the amount of $\Delta^{9,10}$-octalin increases from 52% when pure ethylamine is the solvent to 80–82% when the solvent is an ethylamine-dimethylamine mixture. As another example, the reduction of *t*-butylbenzene with lithium in pure ethylenediamine produces a product containing 70% of 1-*t*-butylcyclohexene.[7] When a mixture of ethylenediamine and morpholine is used as the reaction solvent, the product contains 84% of 1-*t*-butylcyclohexene.[8]

The separation procedure[4] described in this preparation illustrates the *in situ* generation of a solution of *bis*-(3-methyl-2-butyl)-borane in tetrahydrofuran and use of this sterically hindered borane to react with a trisubstituted olefin ($\Delta^{1,9}$-octalin) in preference to a more hindered tetrasubstituted olefin ($\Delta^{9,10}$-octalin).[9] The alkylborane adduct produced from $\Delta^{1,9}$-octalin is oxidized with alkaline hydrogen peroxide to form 1-decalol, which is easily separated from the olefinic product.

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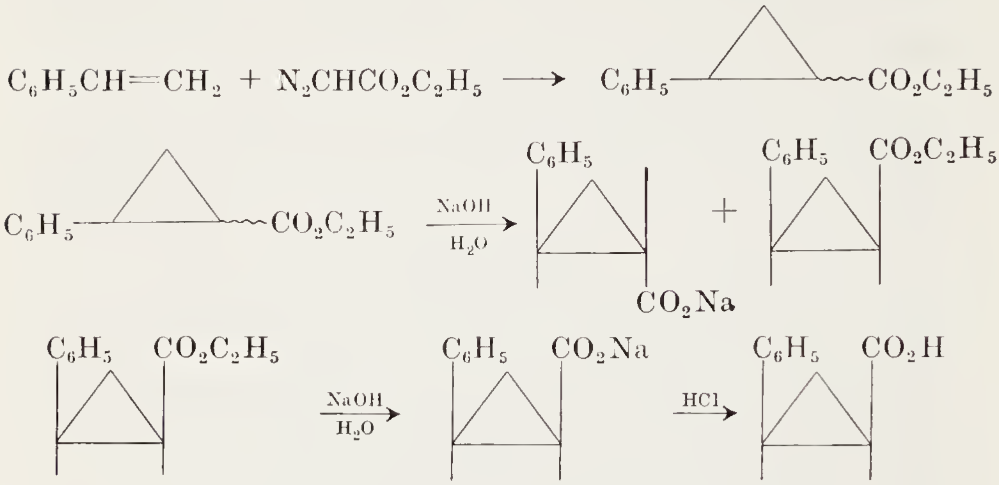
cis-2-PHENYLCYCLOPROPANECARBOXYLIC ACID

(Cyclopropanecarboxylic acid, 2-phenyl-, *cis*-)



Submitted by Carl Kaiser, Joseph Weinstock,
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Checked by William E. Parham, Wayland E. Noland,
Paul Cahill, and Thomas S. Straub

1. Procedure

A. *Ethyl cis- and trans-2-phenylcyclopropanecarboxylate.* Five hundred milliliters of xylene (Note 1) is heated to reflux in a 2-l. flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser. A solution of 179 g. (1.57 moles) of ethyl diazoacetate[2] (Note 2) and 163 g. (1.57 moles) of styrene (Note 3) is placed in the dropping funnel and is added dropwise to the refluxing and stirred xylene over a period of 90 minutes. After addition is complete, the solution is stirred and heated at the reflux temperature for an additional 90 minutes (Note 4). Xylene is removed under reduced pressure and the residual red oil is distilled through a short Vigreux column. The fraction boiling at 85–93° (0.5 mm.) is collected. The weight of colorless product (n_D^{26} 1.5150, n_D^{20} 1.5166) is 155 g. (52% yield) (Notes 5 and 6).

B. *cis-2-Phenylcyclopropanecarboxylic acid.* In a 1-l. three-necked flask equipped with a dropping funnel, stirrer, and a short Vigreux column (Note 7) to which is attached a partial take-off distilling head with reflux condenser is placed 155 g. (0.81 mole) of ethyl *cis*- and *trans*-2-phenylcyclopropanecarboxylate, 200 ml. of ethyl alcohol, 65 ml. of water, and 24.5 g. (0.61 mole) of sodium hydroxide pellets (Note 8). The mixture is heated at the reflux temperature for 5 hours during which time 200 ml. of ethyl alcohol is slowly distilled and collected and is replaced by an equal volume of water added through the dropping funnel. The heat is then removed, 250 ml. of water and 150 ml. of benzene are added, and the mixture is stirred for 2–3 minutes. The layers are separated and the aqueous layer is washed with two 50-ml. portions of benzene (Note 9).

The benzene extracts are placed in the apparatus used above, and 130 ml. of water and 13 g. (0.32 mole) of sodium hydroxide pellets are added. Benzene (200 ml.) is distilled and then the 200 ml. of ethanol obtained in the initial hydrolysis is added. The reflux-distillation process is continued for 5 hours during which time 250 ml. of distillate is obtained. The mixture is then cooled and 65 ml. of benzene and 30 ml. of concentrated hydrochloric acid are added. The layers are separated and the aqueous solution is washed twice with 35-ml. portions of benzene. The combined benzene extract is concentrated and dried by distillation of 90 ml. of benzene. The hot concentrate is decanted from a trace of salt, 70 ml. of petroleum ether is added, and the resulting solution is stored overnight at 0°. The solid, obtained from the cold mixture by filtration, is washed with a small amount of a cold 50–50 mixture of benzene and petroleum ether. The product, *cis*-2-phenylcyclopropanecarboxylic acid, weighs 19.5–23.8 g. (14.6–20.7% yield based on mixed ester used or 38–46.4%, based on the *cis* ester in the mixture) (Note 10) and melts at 106–109° (Note 11). An additional 2–3 g. of *cis* acid may be obtained by concentrating the mother liquors to low volume, adding petroleum ether, and chilling the resulting solution for several days.

2. Notes

1. The checkers used xylene purified by distillation from sodium.

2. Ethyl diazoacetate is available from Aldrich Chemical Co., 2371 North 30th Street, Milwaukee, Wisconsin. *Diazoacetic esters are potentially explosive and therefore must be handled with caution.*[2]

3. Redistilled styrene, b.p. 52–3° (28 mm.) was used by the submitters. The checkers used reagent grade styrene obtained from Eastman Organic Chemicals without further purification.

4. Refluxing was discontinued after nitrogen evolution was complete.

5. Vapor phase chromatography of several samples of mixed ester revealed a composition of 55–65% *trans*, 30–40% *cis*-ester, and 5% impurities.

6. The checker obtained 204 g. of product (68% yield), n_D^{26} 1.5160, with the approximate composition 39% *cis*–60% *trans*-ester.

7. The checkers used a 50-cm. Vigreux column.

8. The amount of base used is 0.75 mole per mole of mixed esters. This is slightly more than necessary to saponify all the *trans* ester present. Since the *trans* ester is saponified more rapidly than the *cis* ester, this affords an effective separation of the isomer. This procedure is a modification of that of Walborsky and Plonsker.[3]

9. *trans*-2-Phenylcyclopropanecarboxylic acid may be obtained from the aqueous solution in the following way. The aqueous solution is treated with 65 ml. of concentrated hydrochloric acid and the mixture is then extracted with one 130-ml. portion of benzene and two 20-ml. portions of benzene. The carefully separated benzene layers are combined and dried by distilling 100 ml. of benzene. The resulting solution is decanted from the small amount of salt present and diluted with 200 ml. of petroleum ether. The resulting solution is cooled at 0° overnight, and the precipitate is collected and washed with a small amount of a 50–50 mixture of cold petroleum ether and benzene. There is obtained 63–65 g. (80% based on *trans* ester originally present) of needles, m.p. 87–93°. Recrystallization of this product several times from a carbon tetrachloride-petroleum ether mixture gives pure *trans* acid, m.p. 93°.

10. The submitters obtained 25–28 g. of *cis* acid (19–21% based on the mixed ester used).

11. Burger and Yost[4] reported m.p. 106–107° for pure *cis*-2-phenylcyclopropanecarboxylic acid and m.p. 93° for pure *trans*-2-phenylcyclopropanecarboxylic acid.

3. Discussion

The described method is a modification of that described by Walborsky and Plonsker.[3] It is based on the more rapid hydrolysis, due to less steric hindrance, of the *trans* over the *cis* ester. The *cis* acid has also been obtained by fractional crystallization of the mixed acids.[4]

The present method offers a convenient preparation of *cis*-2-phenylcyclopropanecarboxylic acid that is amenable to large-scale work. The process above has been carried out in the laboratories of the submitters on a twentyfold scale with essentially the same results. The method also provides an example of the separation of two isomers based on differences in reaction rate.

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1-PHENYL-1,4-PENTADIYNE AND 1-PHENYL-1,3-PENTADIYNE

(1,4-Pentadiyne, 1-phenyl, and 1,3-Pentadiyne, 1-phenyl)

$$C_6H_5C{\equiv}CMgBr + BrCH_2C{\equiv}CH \xrightarrow[\text{THF}]{Cu_2Cl_2}$$

$$C_6H_5C{\equiv}CCH_2C{\equiv}CH \xrightarrow[C_2H_5OH]{\text{NaOH}} C_6H_5C{\equiv}CC{\equiv}CCH_3$$

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Checked by Marion F. Habibi and Richard E. Benson

1. Procedure

A. *Phenylethynylmagnesium bromide.* In a 1-l. four-necked flask fitted with a sealed mechanical stirrer, a reflux condenser carrying calcium chloride and soda lime tubes, a nitrogen gas inlet, and a dropping funnel is placed 19 g. (0.81 mole) of magnesium. The flask is flushed with prepurified nitrogen, the stirrer is started, and ethyl bromide (109 g., 1 mole) in 350 ml. of anhydrous tetrahydrofuran (Note 1) is added. After the magnesium has dissolved (Note 2), 102 g. (1 mole) of phenylacetylene (Note 3) in 150 ml. of tetrahydrofuran is added over a period of *ca.* 30 minutes at a rate to maintain gentle reflux (Note 4). The reaction mixture is then heated at reflux for *ca.* 1.5 hours (Note 5).

B. 1-*Phenyl*-1,4-*pentadiyne*. Anhydrous cuprous chloride (2 g.) is added to the flask and heating under reflux is continued for 20 minutes. At this point 96 g. (0.81 mole) of propargyl bromide in 120 ml. of tetrahydrofuran (Notes 1 and 6) is added during 30–40 minutes at a rate to maintain gentle refluxing. The mixture, containing a yellow solid, is heated another 30–40 minutes, allowed to cool to ambient temperature, and is poured slowly into 2 l. of ice-water slush containing 50 ml. of concentrated sulfuric acid. The whole mixture, which should be acidic at this point, is stirred thoroughly and extracted five times with 200-ml. portions of ether (Note 7). The ether extracts are combined and washed with 100-ml. portions of water until the water layer is no longer acid to litmus paper (3–4 washings usually required). The ether layer is dried with magnesium sulfate overnight, separated from the desiccant, and the ether removed by distillation.

The product is distilled under nitrogen using a 25-cm. Vigreux column (Notes 8 and 9). After removal of unreacted propargyl bromide and phenylacetylene, 1-phenyl-1,4-pentadiyne is collected as the main fraction, b.p. 64–66° (0.45 mm), $n^{25}\text{D}$ 1.5713. The yield is 51–64 g. (45–57%) (Notes 9 and 10). The colorless product is best stored under nitrogen at *ca.* −78°. The n.m.r. spectrum (60 mHz., neat, external tetramethylsilane reference) shows a triplet at 1.76 p.p.m., a doublet centered at 2.92 p.p.m., and a multiplet at 6.87 p.p.m. of relative intensities 1:2:5, respectively (Note 11).

C. 1-*Phenyl*-1,3-*pentadiyne*. A flask containing a magnetic stirrer and a solution of 2 g. of sodium hydroxide in 50 ml. of ethanol is flushed with nitrogen and 10 g. (0.07 mole) of 1-phenyl-1,4-pentadiyne is added. The flask is stoppered and the contents are stirred for *ca.* 2 hours. The brown solution is then poured into 200 ml. of water and the mixture extracted four times with 50-ml. portions of ether. The extracts are combined and washed with two 50-ml. portions of water, and the ether layer is dried with magnesium sulfate. The mixture is filtered, the ether is removed by distillation, and the product is distilled as described in Part B. 1-Phenyl-1,3-pentadiyne is obtained as a colorless oil, b.p. 62° (0.15 mm.), $n^{25}\text{D}$ 1.6324. The yield is 5.4–7.5 g. (54–75%). The n.m.r. spectrum (60 mHz., neat, external tetramethylsilane reference) shows a singlet at 1.47 p.p.m. and a multiplet at 6.87 p.p.m. of relative intensities 3:5, respectively (Note 11).

2. Notes

1. Reagent grade tetrahydrofuran available from Fisher Scientific Company was used by the checkers. For warning regarding the purification of tetrahydrofuran see *Org. Syntheses,* **46,** 105 (1966).

2. The flask may be warmed to hasten the dissolution of magnesium.

3. Phenylacetylene was distilled under nitrogen, b.p. 91–92° (17.5 mm.).

4. An ice-water bath should be kept at hand to cool the flask in the event the rate of refluxing becomes too great.

5. If the reaction is slow, the solution is kept at reflux overnight under an atmosphere of nitrogen. More tetrahydrofuran (50 ml.) may be added if stirring becomes difficult. It is desirable that procedure B follow A as soon as possible.

6. Propargyl bromide was redistilled, b.p. 82–83°.

7. The diyne discolors at room temperature and on exposure to air. Therefore it is desirable to proceed without delay in the workup steps.

8. The checkers found it advantageous to do a crude preliminary distillation using a vapor-bath still. The resulting distillate can be redistilled using a spinning band column. This

procedure appeared to avoid an exothermic reaction that occurred when the bath temperature rose above 110° (Note 9).

9. After the 1,4-diyne has distilled, overheating the pot contents is to be avoided since an exothermic reaction can occur.

10. The checkers observed yields of 44–50% in conducting the reaction on a scale one-half that described here.

11. Where they differ from those reported previously,[2] the values of the physical properties are those obtained by the checkers.

3. Discussion

The synthetic route described here has been used for various "skipped" diynes and related 1,3-diynes, among which are precursors or analogs of naturally occurring polyynes.[2] The cuprous chloride-promoted coupling reaction in tetrahydrofuran provides the best and often the sole route to the 1,4-diynes.[2] From these it is simple to proceed to the 1,3-diyne, possibly with a stop on the way at the isomeric allene.[2,6] Because all of these compounds appear to be sensitive, *e.g.*, to heat and oxygen, the relatively mild conditions of their syntheses are noteworthy.

1-Phenyl-1,4-pentadiyne has been prepared by coupling in tetrahydrofuran without a copper chloride catalyst in 22% yield,[3] and in ether with a copper chloride catalyst in 28% yield.[4] In general, the coupling of propargyl halides with various metallic acetylides, *e.g.*, sodium, silver, gives 1,4-pentadiynes in low yields at best.[2] Strongly basic reactants such as alkali acetylides or basic conditions for workup and purification, *e.g.*, column chromatography over alumina, promote the disappearance of the 1,4-diyne by isomerization.[2,6] The evolution of the present method, which emphasizes the use of tetrahydrofuran as solvent, a copper(II) salt, a short coupling time, and neutral reaction and workup conditions, has been described in detail.[2]

1-Phenyl-1,3-pentadiyne has been prepared by the dehydrobromination of the corresponding butadiene tetrabromide.[5] Other unsymmetrical 1,3-diynes have been prepared by scheme

1.[7] It is, of course, typical of crossed-coupling reactions that

$$\begin{array}{c} R{-}C{\equiv}C{-}H \\ + \\ R'{-}C{\equiv}C{-}Br \end{array} \xrightarrow[\text{base}]{Cu^+} R{-}C{\equiv}C{-}C{\equiv}C{-}R' \qquad (1)$$

some should proceed as desired in (2),[2] and that others should go astray, as in (3).[2] The conversion of 1,4- to 1,3-diynes by

$$C_6H_5(C{\equiv}C)_2MgBr + 4\text{-}CH_3C_6H_4SO_2CH_2C_6H_5 \rightarrow C_6H_5(C{\equiv}C)_2CH_2C_6H_5 \qquad (2)$$

strong base in ethanol or methanol at reflux has been described.[3,4] As judged by the isomerization rates in sodium

$$C_6H_5(C{\equiv}C)_2MgBr + C_6H_5CH_2Br \xrightarrow{Cu_2Cl_2} (C_6H_5CH_2)_2 \qquad (3)$$

ethoxide-ethanol, heating appears to be unnecessary. Typical rate constants are given in (4).[6]

$$C_6H_5C{\equiv}CCH_2C{\equiv}CH + C_2H_5O^- \xrightarrow[26^\circ]{1.43\ M^{-1}\,sec^{-1}} C_6H_5C{\equiv}C{-}CH{=}C{=}CH_2 \xrightarrow[26^\circ]{0.47\ M^{-1}\,sec^{-1}} C_6H_5C{\equiv}C{-}C{\equiv}C{-}CH_3 \qquad (4)$$

The present route to conjugated diynes is the method of choice *if* the corresponding skipped diyne or allene is available.[2,6] With naturally occurring polyynes this is often the case. Depending on the 1,4-diyne, the base-catalyzed isomerization may be successfully stopped (by acidification) to yield the intermediate allenylacetylene. Since the isolation of the allene may or may not be desired, it seems prudent to monitor the progress of isomerization of new 1,4-diynes, *e.g.*, by n.m.r., and establish the approximate lifetimes of transient species. In this way some allenes as well as conjugated diynes may be obtained.[6]

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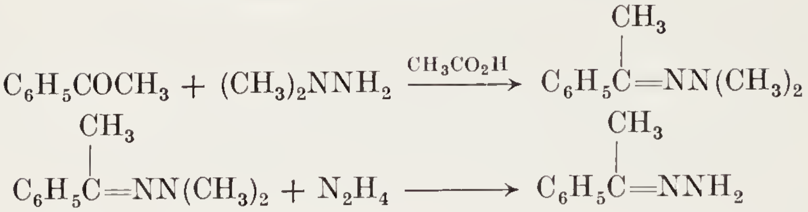
PREPARATION OF HYDRAZONES: ACETOPHENONE HYDRAZONE



$$C_6H_5COCH_3 + (CH_3)_2NNH_2 \xrightarrow{CH_3CO_2H} C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}{=}NN(CH_3)_2$$

$$C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}{=}NN(CH_3)_2 + N_2H_4 \longrightarrow C_6H_5\overset{\overset{\displaystyle CH_3}{|}}{C}{=}NNH_2$$

Submitted by G. R. Newkome[1] and D. L. Fishel[2]
Checked by G. Swift and W. D. Emmons

1. Procedure

Caution! Hydrazines are toxic and should be handled in a hood. Anhydrous hydrazine is extremely reactive with oxidizing agents (including air) and should always be used behind a protective screen.

A. *Acetophenone N,N-dimethylhydrazone.* A mixture of acetophenone (12.0 g., 0.1 mole), anhydrous N,N-dimethylhydrazine (18.0 g., 0.3 mole) (Note 1), absolute ethanol (25 ml.) and glacial acetic acid (1 ml.) (Note 2) is heated at reflux for 24 hours. During this period the colorless solution becomes bright yellow. The volatile reactants and solvent are removed under reduced pressure. The residual oil is fractionally distilled through a 10-cm. Vigreux column to give a small forerun of unreacted acetophenone, b.p. 30–40° (0.15 mm.), followed by 14.6–15.2 g. (90–94%) of acetophenone N,N-dimethylhydrazone, b.p. 55–56° (0.15 mm.), n^{25}D 1.5443 (Notes 3 and 4).

B. *Acetophenone hydrazone.* A mixture of acetophenone N,N-dimethylhydrazone (8.1 g., 0.05 mole) and anhydrous hydrazine (6.4 g., 0.20 mole) (Note 5) in absolute ethanol (15 ml.) is heated at reflux until the reaction mixture turns colorless (Note 6). The volatile materials are removed on a rotary evaporator without allowing the flask temperature to rise above 20° (Note 7). The colorless residual acetophenone hydrazone, which solidifies as the last traces of solvent are removed, weighs 6.5–6.6 g. (97–99%) and is sufficiently pure for most purposes, m.p. 24–25° (Notes 8 and 9).

2. Notes

1. Anhydrous N,N-dimethylhydrazine obtained from Matheson, Coleman and Bell is used directly. It can also be prepared by the method of Hott, *Org. Syntheses*, Coll. Vol. **2,** 213 (1943).

2. It is not necessary to use glacial acetic acid as catalyst, but without it the reaction time required for completion is prolonged.

3. Physical constants previously reported:[3] b.p. 100.5–102° (10 mm.), $n^{25}\text{D}$ 1.5455.

4. This method has been used to prepare various N,N-dimethylhydrazones in 70–99% yield.[4]

5. A good commercial grade of anhydrous hydrazine (Eastman Organic Chemicals) is satisfactory.

6. The reaction time for complete conversion is usually less than 24 hours. A convenient "end point" is the visual color change from bright yellow to colorless or very pale yellow.

7. It is of utmost importance that the flask temperature during the removal of the volatile materials be kept below 20° in order to minimize possible azine formation by decomposition of the hydrazone.

8. The reported melting points are 16–20°,[5] 22°,[6] 24–25°,[4,7] and 26°.[7]

9. Acetophenone hydrazone can be stored at temperatures below 0° for indefinite periods of time.

3. Discussion

The formation of acetophenone hydrazone has been accomplished by heating acetophenone with hydrazine or hydrazine hydrate,[7–10] by heating acetophenone azine with anhydrous hydrazine,[6,11] by the reaction of α-dimethylaminoacetophenone with hydrazine,[5] and by the present method.[4]

This synthetic process is applicable to the preparation of most hydrazones from aldehydes and ketones. The two-step preparation offers several distinct advantages over the one-step method:[6,9] (1) the yield of both steps is high; (2) the product is not contaminated with azine; (3) the isolated product is pure enough to be used in subsequent reactions without further purification. This method excels in the preparation of unstable liquid or low-melting hydrazones over the common methods of preparation.

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2. Department of Chemistry, Kent State University, Kent, Ohio 44240.
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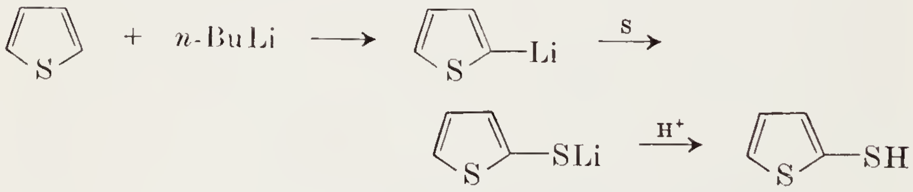
2-THIOPHENETHIOL

(2-Thienyl mercaptan)



Submitted by E. Jones[1] and I. M. Moodie
Checked by E. J. Corey and Joel I. Shulman

1. Procedure

In a 3-l. three-necked flask fitted with a mechanical stirrer, a 600-ml. dropping funnel, and filled with dry nitrogen are placed 500 ml. of tetrahydrofuran (distilled from lithium aluminum hydride) and 53 ml. (56.5 g., 0.67 mole) of thiophene. This mixture is stirred under nitrogen and cooled to −40° by a dry ice-acetone bath while 490 ml. (0.66 mole) of 1.35 *M* *n*-butyllithium in pentane (Notes 1 and 2) is added over a 5-minute period *via* the dropping funnel. The temperature of the mixture is held between −30° and −20° for 1 hour and then is lowered to −70° by the addition of dry ice to the bath. Powdered sulfur crystals (20.4 g., 0.67 g. atom) are added in one aliquot to the stirred mixture. After 30 minutes the temperature is allowed to rise to −10°, whereupon the yellow solution is carefully poured into 1 l. of rapidly stirred ice water to dissolve the lithium salt of the thiol and to destroy any unreacted 2-thienyllithium. The pentane layer is extracted with three 100-ml. portions of water. These aqueous extracts are combined with the aqueous layer, the whole chilled and carefully acidified with 4 *N* sulfuric acid (Note 3). This aqueous phase is immediately extracted with three 200-ml. portions of ether (Note 4). The combined ether extracts are washed twice with 100-ml. portions of water to remove acid and remaining tetrahydrofuran and then dried over anhydrous sodium sulfate. After removal of ether, the residual golden-brown oil is purified by distillation at reduced pressure. The portion boiling at 53–56° (5 mm.) is collected as 2-thiophenethiol, a yellow oil, $n^{25}{}_{\mathrm{D}}$ 1.6110. The yield is 49.5–53.5 g. (65–70%).

2. Notes

1. The checkers obtained *n*-butyllithium from the Foote Mineral Co., Exton, Pennsylvania. The concentration of *n*-butyllithium was determined by the method of Gilman and Haubein.[2] This reagent is conveniently transferred to a previously calibrated addition funnel under nitrogen pressure through a short length of inert (*e.g.*, Teflon) tubing.

2. The submitters employed *n*-butyllithium prepared by the method of Jones and Gilman.[3] The *n*-butyllithium solution so prepared was filtered to remove finely divided lithium using an apparatus previously described.[4]

3. The general procedure is similar to that described by Gronowitz[5] in the preparation of 3-thiophenethiol, the principal differences being the use of tetrahydrofuran-pentane solvent and the omission of a 10% potassium hydroxide extraction before acidification with sulfuric acid. This omission leads to higher yields of thiol.

4. Undue delay in the ether extraction of the thiol has been found to result in reduced yields.

3. Discussion

Houff and Schuetz[6] have prepared 2-thiophenethiol by two different routes. One involves the sulfurization of 2-thienylmagnesium bromide followed by acidification to give the thiol. The other method is an *in situ* reduction of 2-thienylsulfonyl chloride with zinc dust and sulfuric acid. Gronowitz[5] has prepared the isomeric 3-thiophenethiol by sulfurization of 3-thienyllithium which was obtained by a transmetalation of 3-bromothiophene with *n*-butyllithium.

This method is based on the known reactivity of the 2-position of thiophene so that the desired 2-thiophenethiol may be prepared in good yield by direct substitution of thiophene. 2-Chloro-5-thiophenethiol may also be prepared by this method in 59% yield from 2-chlorothiophene.[7]

Direct substitution in the 3-position of the thiophene ring is difficult and can be achieved only by activation of this reaction site. Thus the isomeric 3-thiophenethiol may be prepared by this general method starting from a 3-halogenothiophene. For example, this thiol may be obtained from 3-bromothiophene in 63% yield.[5]

The procedure outlined above also offers a general method for the synthesis of alkyl and aryl thiols starting from the appropriate halides. Thus thiophenol may be obtained in 62% yield by lithiation and sulfurization of bromobenzene.[8]

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TRIMETHYLSILYL AZIDE

$$(CH_3)_3SiCl + NaN_3 \rightarrow (CH_3)_3SiN_3 + NaCl$$

Submitted by L. Birkofer and P. Wegner[1]
Checked by R. F. Merritt and W. D. Emmons

1. Procedure

Caution! This reaction should be conducted behind a safety screen in a hood. If the system is not completely dry, the presence of toxic hydrazoic acid is probable.

A 1-l. three-necked flask fitted with a stirrer, reflux condenser equipped with a drying tube, and addition funnel provided with a pressure-equalizer arm is dried in a 100° oven and assembled while warm. The warm apparatus is immediately purged with dry nitrogen. It is convenient to introduce the nitrogen at the top of the addition funnel. The flask is then charged with 81 g. (1.25 moles) of sodium azide (Note 1) and 500 ml. of freshly distilled diethyleneglycol dimethyl ether (Note 2). A simple distillation apparatus is then dried in the oven and assembled while warm under a slow nitrogen purge. The distillation flask is charged with 112 g. of trimethylchlorosilane (Note 3), and after a forerun of approximately 2 g. the remaining material is distilled (b.p. 57–58°) directly into the addition funnel of the reaction flask. During this distillation it is convenient to disconnect the nitrogen stream from the top of the addition funnel and introduce it into the distillation flask. After the distillation is complete, the distillation apparatus is disconnected and the nitrogen stream is again introduced at the top of the addition funnel. The trimethylchlorosilane (108.6 g., 1.0 mole) (Note 4) is then added rapidly to the sodium azide slurry and this mixture is stirred at 70° for 60 hours. During this period the nitrogen flow is terminated (Note 5).

After the heating period is complete, the nitrogen stream is again initiated and the mixture is cooled to 30°. The addition funnel and reflux condenser are replaced with two gas inlet tubes with stopcocks. One inlet tube is connected to the nitrogen source and the other to a standard vacuum trap with at least 150 ml. capacity. A vacuum source of 15–20 mm. is attached to the trap after the latter is cooled to −78°. The product is then distilled at 30° (15 mm.) into the trap. Slight heating is necessary to maintain 30°, and rapid stirring should be continued throughout the stripping operation. Removal of volatile product is complete within 5 hours under these conditions. The entire system is then slowly pressurized to atmospheric pressure with nitrogen and the product redistilled through a 5-cm. Vigreaux column. From a total of 121 g. of crude flash distillate are obtained 4.0 g. of forerun and 98 g. (85% yield) of pure trimethylsilyl azide, b.p. 95–99°. During the distillation the pot temperature is maintained at 135–140° with a thermostated oil bath. The pot residue contains 19 g. of diethyleneglycol dimethyl ether with traces of trimethylsilyl azide. The purity of the product cut as established by n.m.r. (CCl_4) is 98%. A single peak at 13 cps. downfield from tetramethylsilane is observed, the only impurity being siloxane hydrolysis products. Trimethylchlorosilane is conspicuous by its absence.

2. Notes

1. Sodium azide was obtained from Alpha Inorganics, Inc., Beverly, Massachusetts, and the freshly opened material was used without further purification or drying.

2. Diethyleneglycol dimethyl ether from Aldrich Chemical Co. was distilled under a nitrogen atmosphere and the fraction boiling at 161–2° was used.

3. The trimethylchlorosilane was obtained from Pennisula Chem-research Corp., Gainesville, Florida.

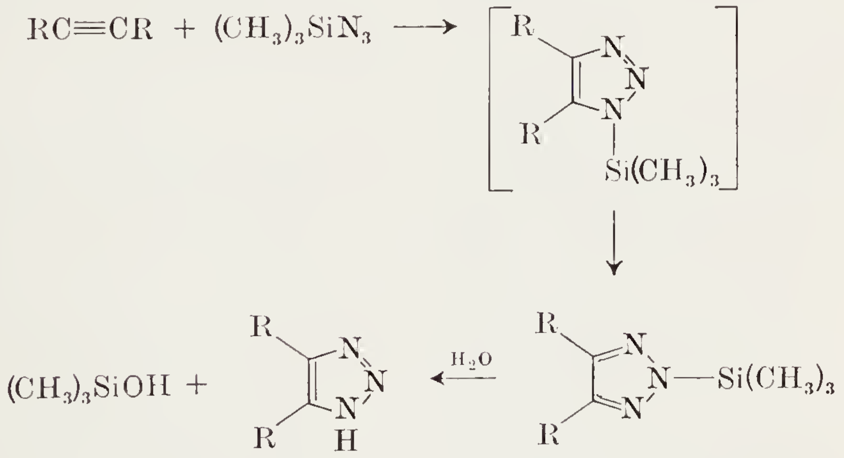
4. It is undesirable to reweigh the trimethylchlorosilane in the addition funnel because moisture contamination is possible. An excess of sodium azide is used in this preparation and the exact amount of the silane used is not critical.

5. If the nitrogen flow is maintained during the heating period, the volatile materials will be swept out and the yield will be reduced.

3. Discussion

Trimethylsilyl azide has been prepared by the thermolysis of 1-trimethylsilyl-5-trimethylsilylaminotetrazole, by reaction of hydrazoic acid with hexamethyl-disilazane, and by reaction of trimethylchlorosilane with sodium azide.[2] With a suitable solvent and anhydrous conditions the last procedure is the method of choice and has been extended to other trialkyl and triarylsilyl azides.[3]

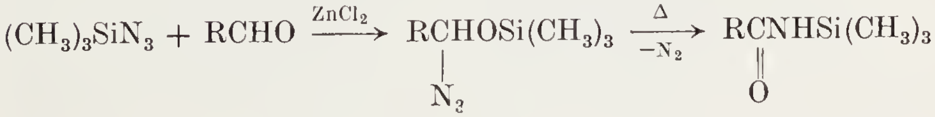
Unlike hydrazoic acid, trimethylsilyl azide is thermally quite stable. Even at 200° it decomposes slowly and without explosive violence. Accordingly it is a very convenient and safe substitute for hydrazoic acid in many reactions. A notable example is the cycloaddition of hydrazoic acid to acetylenes which is a general route to substituted triazoles.[4] The reaction of trimethylsilyl azide with acetylenes is also a general reaction from which the 2-trimethylsilyl-1,2,3-triazoles may be obtained in good yield.[5] On hydrolysis these adducts are converted under mild conditions to the parent alkyl 1,2,3-triazoles.[5]



Another interesting application for trimethylsilyl azide is as a convenient preparation of trialkyl- or triarylphosphinimines first prepared by Appel and Hauss using chloramine.[6] This

$$R_3P + (CH_3)_3SiN_3 \xrightarrow{-N_2} R_3P{=}NSi(CH_3)_3 \xrightarrow{ROH} R_3P{=}NH$$

synthesis is quite simple and is again dependent for its success on the facile cleavage of the Si—N bond.[7,8] Trimethylsilyl azide



$$(CH_3)_3SiN_3 + RCHO \xrightarrow{ZnCl_2} \underset{\displaystyle N_3}{\underset{|}{RCHOSi(CH_3)_3}} \xrightarrow[-N_2]{\Delta} \underset{\displaystyle O}{\underset{\|}{RCNHSi(CH_3)_3}}$$

also reacts with aldehydes to give the stable adducts, 1-trimethylsiloxyalkyl azides, which on thermolysis yield N-trimethylsilyl amides.[9]

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Names in small capital letters refer to the titles of individual preparations. A number in ordinary boldface type denotes the volume. A page number in boldface italics indicates that the detailed preparative directions are given or referred to; entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations.

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Unchecked Procedures

Received during the period
Sept. 1, 1969-June 30, 1970

In accordance with a new policy adopted by the Board of Editors, which, as noted in the Editor's Preface, is intended to make procedures available more rapidly, all procedures received by the Secretary after Sept. 1, 1969, whether subsequently accepted or rejected for publication in Organic Syntheses, will be made available for purchase at the price of $2 per procedure, prepaid upon request to the Secretary:

Dr. Wayland E. Noland, Secretary
Organic Syntheses
School of Chemistry
University of Minnesota
Minneapolis, Minnesota 55455

Payment must accompany the order. Procedures may be ordered by number and/or title from the list which follows. This list includes all procedures received during the period Sept. 1, 1969-June 30, 1970. It should be emphasized that the procedures which are being made available are unedited and have been reproduced just as they are received from the submitters.

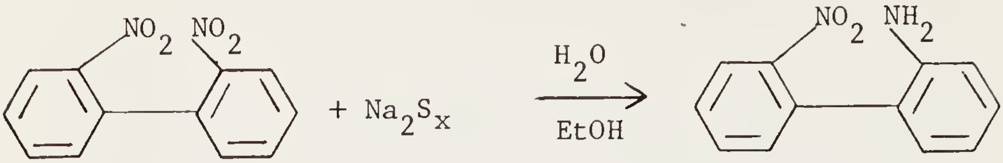
The procedures available have not been checked, and many of them have been or will be rejected for publication in Organic Syntheses either before or after the checking process. For this reason, Organic Syntheses can provide no assurance whatever that the procedures will work as described and can offer no comment as to what safety hazards may be involved. Consequently, more than usual caution should be employed in following the directions in the procedures. Organic Syntheses would welcome, on a strictly voluntary basis, comments from persons who attempt to carry out any of these procedures. For this purpose, a Checker's Report form will be mailed out with each unchecked procedure ordered.

Procedures which have been checked by, or under the supervision of, a member of the Board of Editors will continue to be published in Organic Syntheses, as in the past. It is anticipated that some of the procedures in the list will appear (often in revised form) in Organic Syntheses at some future time.

-Wayland E. Noland

(N69-1) 2-Amino-2'nitrobiphenyl

S. Davis Lewis, Augusta College, Augusta, Ga. 30904

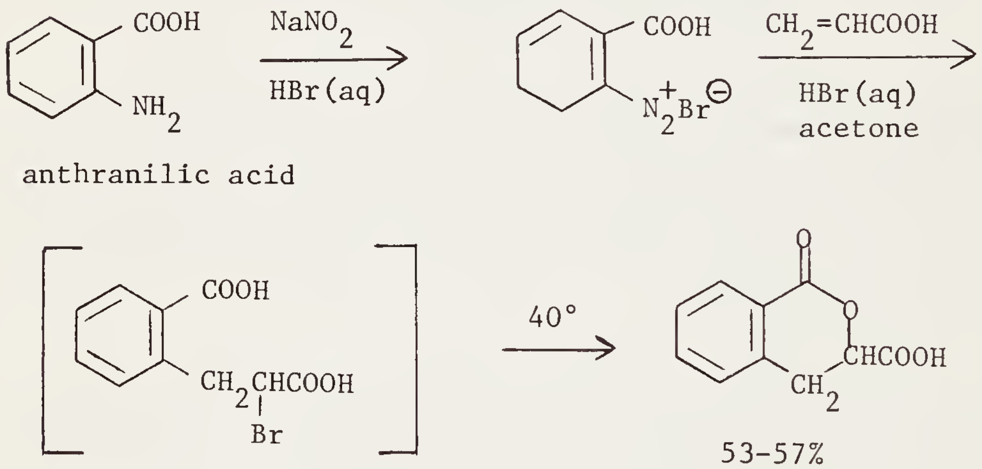

NO_2 NO_2
+ Na_2S_x
H_2O
EtOH
NO_2 NH_2

40-50%

2,2'-dinitrobiphenyl

(N69-2) 1-Oxo-3-isochromancarboxylic Acid

George H. Cleland, Occidental College, Los Angeles, Calif. 90041

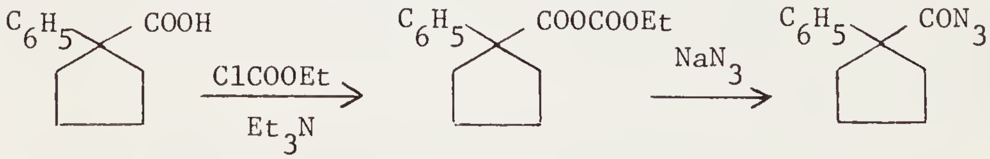

COOH
NH_2
$NaNO_2$
HBr(aq)
COOH
$N_2^+Br^-$
$CH_2=CHCOOH$
HBr(aq)
acetone
COOH
$CH_2CHCOOH$
Br
40°
O
O
CHCOOH
CH_2

anthranilic acid

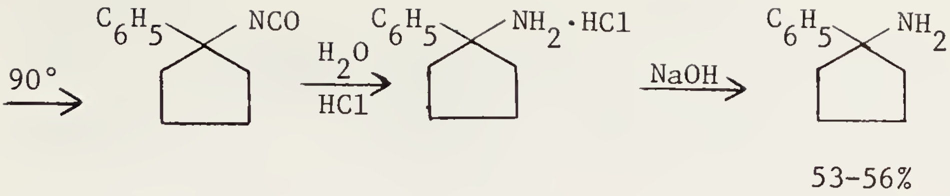
53-57%

(N69-3) 1-Phenylcyclopentylamine

Carl Kaiser and Joseph Weinstock, Smith Kline and French Laboratories, Philadelphia, Pa. 19101


C_6H_5
COOH
ClCOOEt
Et_3N
C_6H_5
COOCOOEt
NaN_3
C_6H_5
CON_3

1-phenylcyclopentane-carboxylic acid


90°
C6H5
NCO
H2O
HCl
C6H5
NH2·HCl
NaOH
C6H5
NH2
53-56%

(D69-1) Azetidine

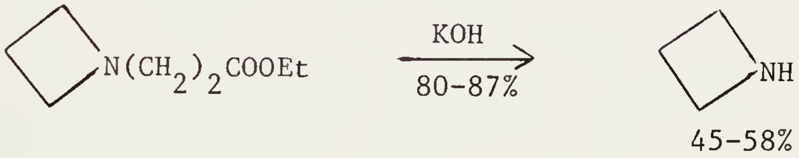
Donald H. Wadsworth, Eastman Kodak Co., Rochester, N. Y.
14650

$HO(CH_2)_3NH_2 + 2CH_2{=}CHCOOEt \xrightarrow[99\%]{}$

3-amino-
1-propanol

$HO(CH_2)_3N(CH_2CH_2COOEt)_2 \xrightarrow[100\%]{SOCl_2}$

$Cl(CH_2)_3N(CH_2CH_2COOEt)_2 \xrightarrow[57\text{-}68\%]{Na_2CO_3}$


N(CH2)2COOEt
KOH
80-87%
NH
45-58%

(D69-2) 1-Benzylazetidine

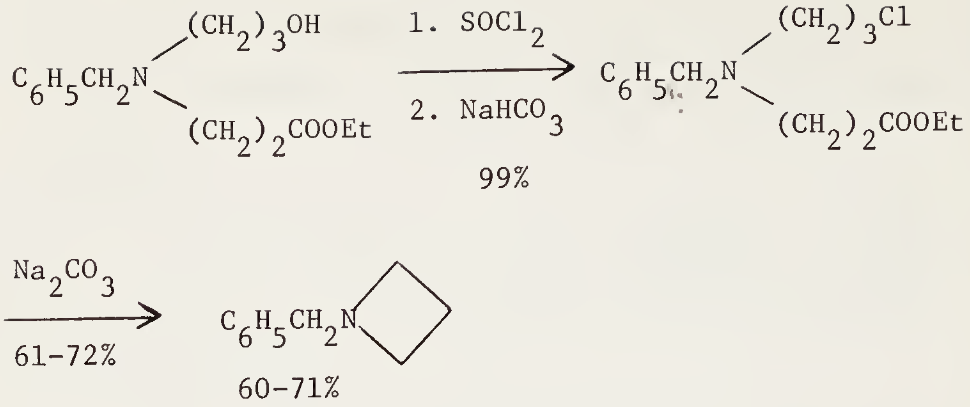
Donald H. Wadsworth, Eastman Kodak Co., Rochester, N. Y.
14650

$C_6H_5CHO + H_2N(CH_2)_3OH \rightarrow \left[C_6H_5CH{=}N(CH_2)_3OH\right]$

3-amino-1-propanol

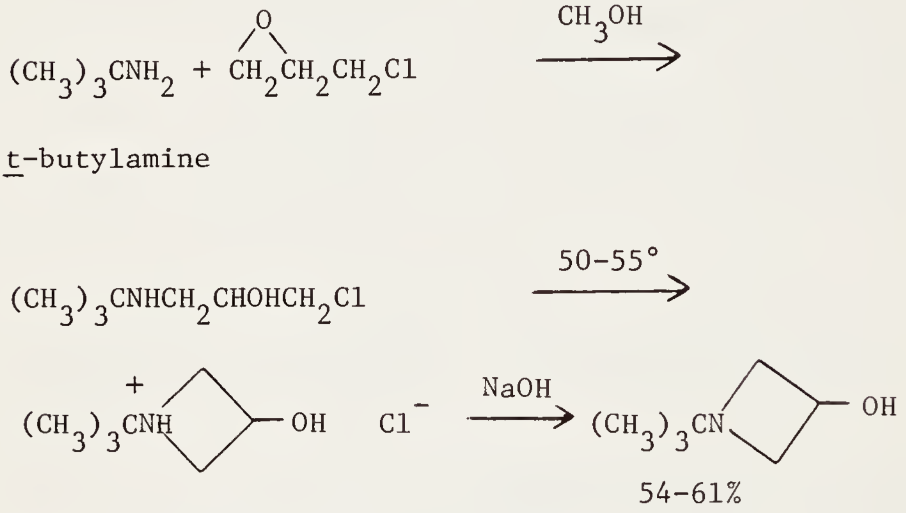
$\xrightarrow[PtO_2]{H_2} C_6H_5CH_2NH(CH_2)_3OH \xrightarrow[100\%]{CH_2{=}CHCOOEt}$

98%


$C_6H_5CH_2N(CH_2)_3OH(CH_2)_2COOEt$
1. $SOCl_2$
2. $NaHCO_3$
99%
$C_6H_5CH_2N(CH_2)_3Cl(CH_2)_2COOEt$
Na_2CO_3
61-72%
$C_6H_5CH_2N$
60-71%

(D69-3) 1-*t*-Butyl-3-azetidinol

V. R. Gaertner, Monsanto Co., St. Louis, Mo. 63166

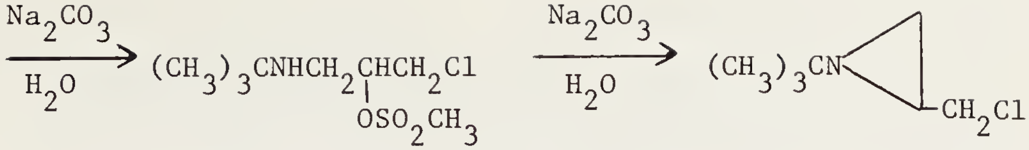

$(CH_3)_3CNH_2$ + $CH_2CH_2CH_2Cl$
O
CH_3OH
t-butylamine
$(CH_3)_3CNHCH_2CHOHCH_2Cl$
50-55°
$(CH_3)_3CNH^+$
OH
Cl^-
NaOH
$(CH_3)_3CN$
OH
54-61%

(D69-4) 1-*t*-Butylchloromethylaziridine

V. R. Gaertner, Monsanto Co., St. Louis, Mo. 63166

$$(CH_3)_3CNHCH_2CHOHCH_2Cl + CH_3SO_2Cl \xrightarrow[C_5H_5N]{CH_3SO_3H}$$

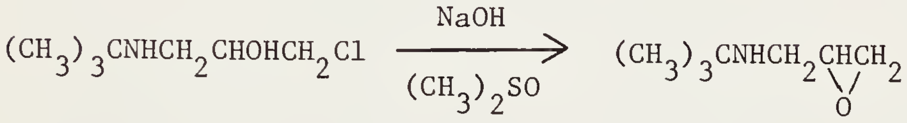
1-*t*-butylamino-
3-chloro-2-propanol


Na2CO3
H2O
(CH3)3CNHCH2CHCH2Cl
OSO2CH3
Na2CO3
H2O
(CH3)3CN
CH2Cl

51-57%

(D69-5) t-Butyl-2,3-epoxypropylamine

V. R. Gaertner, Monsanto Co., St. Louis, Mo. 63166



$$(CH_3)_3CNHCH_2CHOHCH_2Cl \xrightarrow[(CH_3)_2SO]{NaOH} (CH_3)_3CNHCH_2\underbrace{CHCH_2}_{O}$$

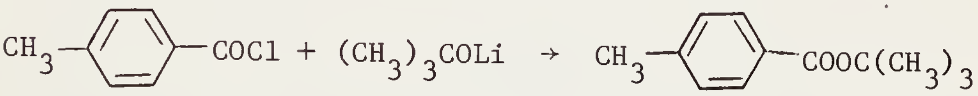
1-t-butylamino-
3-chloro-2-propanol

51-60%

(D69-6) t-Butyl p-Toluate

G. P. Crowther, E. M. Kaiser*, R. A. Woodruff*, and
C. R. Hauser, (*) University of Missouri, Columbia, Mo.
65201

$(CH_3)_3COH + n\text{-}BuLi \rightarrow (CH_3)_3COLi$

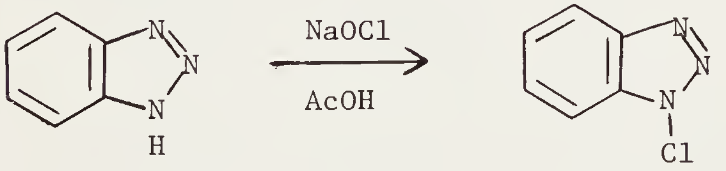

CH3
COCl + (CH3)3COLi →
CH3
COOC(CH3)3

p-toluoyl chloride

79%

(D69-7) 1-Chlorobenzotriazole

M. Keating, C. W. Rees, and R. C. Storr, The Robert
Robinson Laboratories, P.O. Box 147, Liverpool L69 3BX,
England


N
N
N
H
NaOCl
AcOH
N
N
N
Cl

benzotriazole

97%

(Warning: explosive compound)

(D69-8) 1,2-Dichlorohexane

Kurt W. Field and Peter Kovacic, University of Wisconsin, Milwaukee, Wis. 53201

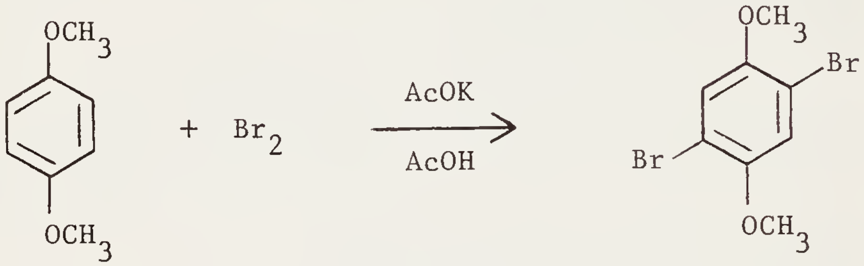
$$CH_3(CH_2)_3CH{=}CH_2 + 2NCl_3 \xrightarrow{CH_2Cl_2} CH_3(CH_2)_3CHClCH_2Cl$$

1-hexene

92-94%

(D69-9) 1,4-Dibromo-2,5-dimethoxybenzene

Girish C. Misra, Lalit M. Pande, and Girish C. Joshi, Defence Research Laboratory (Materials), P.O. Box 320, Kanpur, India

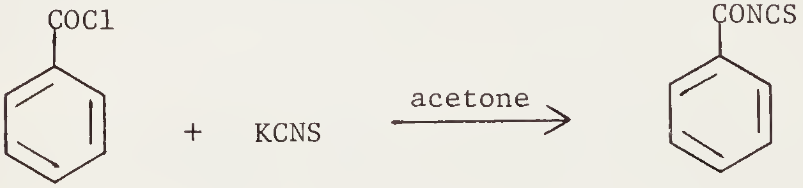

OCH3
OCH3
+ Br2
AcOK
AcOH
OCH3
Br
Br
OCH3

1,4-dimethoxybenzene

72-73%

(Ja70-1) Benzoyl Isothiocyanate

Frederick Kurzer and David R. Hanks, Royal Free Hospital School of Medicine, University of London, London WC1, England

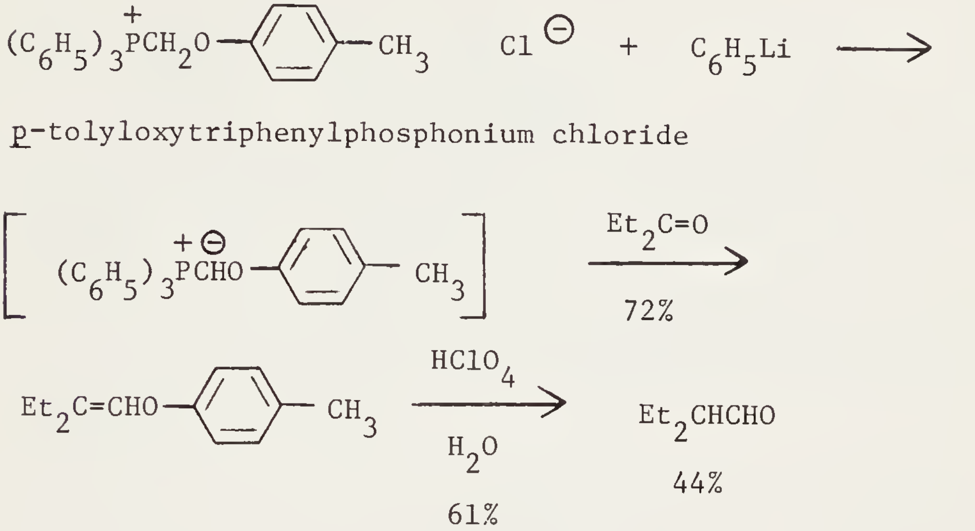

COCl
+ KCNS
acetone
CONCS

benzoyl chloride

65-75%

(Ja70-2) 2-Ethylbutanal

G. Wittig and K. H. Krück, Organisch-Chemisches Institut der Universität, 69 Heidelberg, West Germany



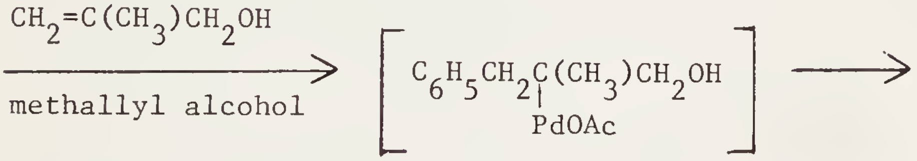
p-tolyloxytriphenylphosphonium chloride

(Ja70-3) 2-Methyl-3-phenylpropionaldehyde

R. F. Heck, Hercules Inc., Wilmington, Del.

$C_6H_5HgOAc + Pd(OAc)_2 \rightarrow [C_6H_5PdOAc]$

phenylmercuric acetate palladium acetate



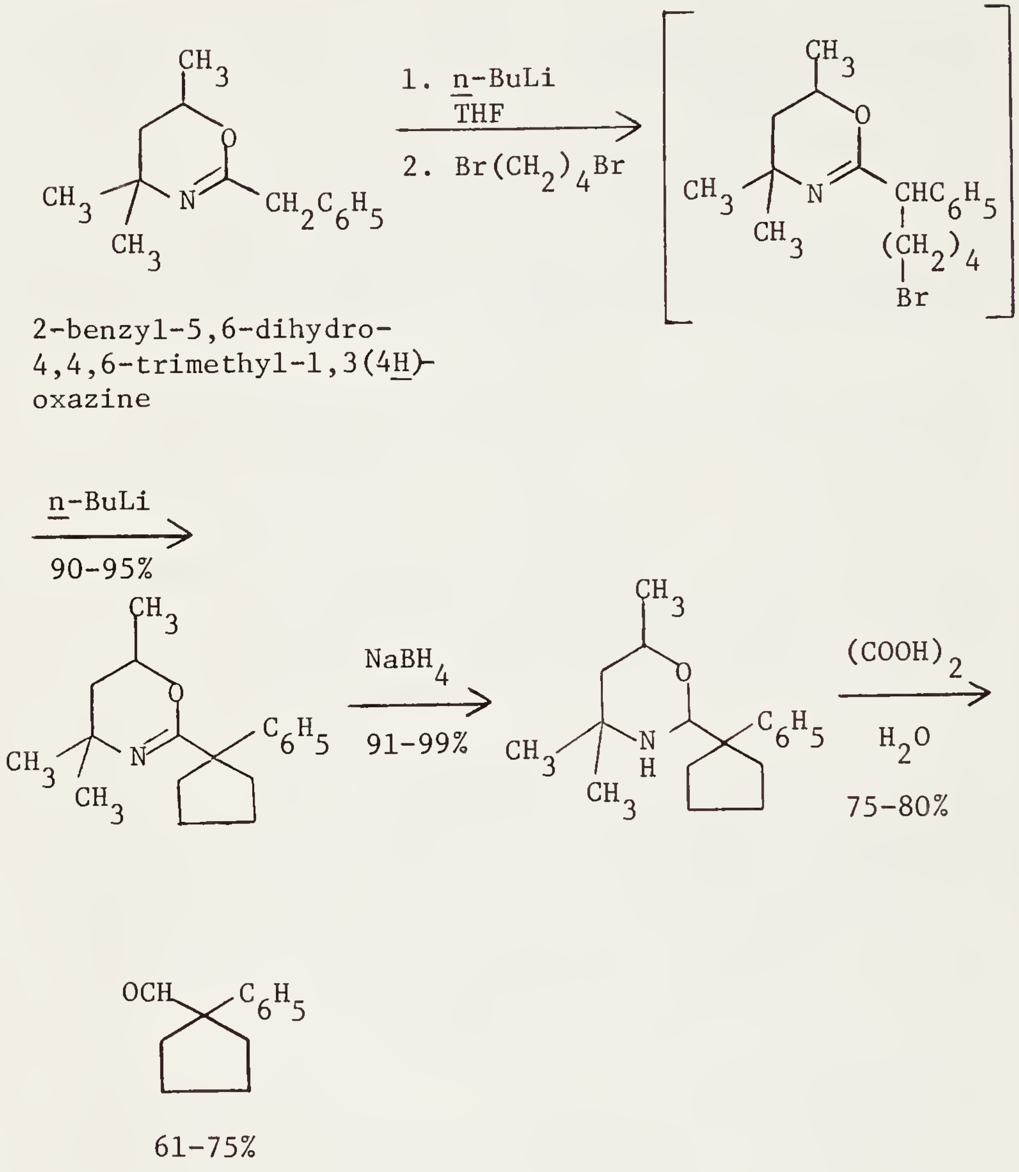
$$\xrightarrow[\text{methallyl alcohol}]{CH_2{=}C(CH_3)CH_2OH} \left[C_6H_5CH_2\underset{\displaystyle PdOAc}{\underset{|}{C}}(CH_3)CH_2OH \right] \longrightarrow$$

$C_6H_5CH_2CH(CH_3)CHO$

55-58%

(Ja70-4) 1-Phenylcyclopentanecarboxaldehyde

Ieva R. Politzer and A. I. Meyers, Louisiana State University in New Orleans, New Orleans, La.

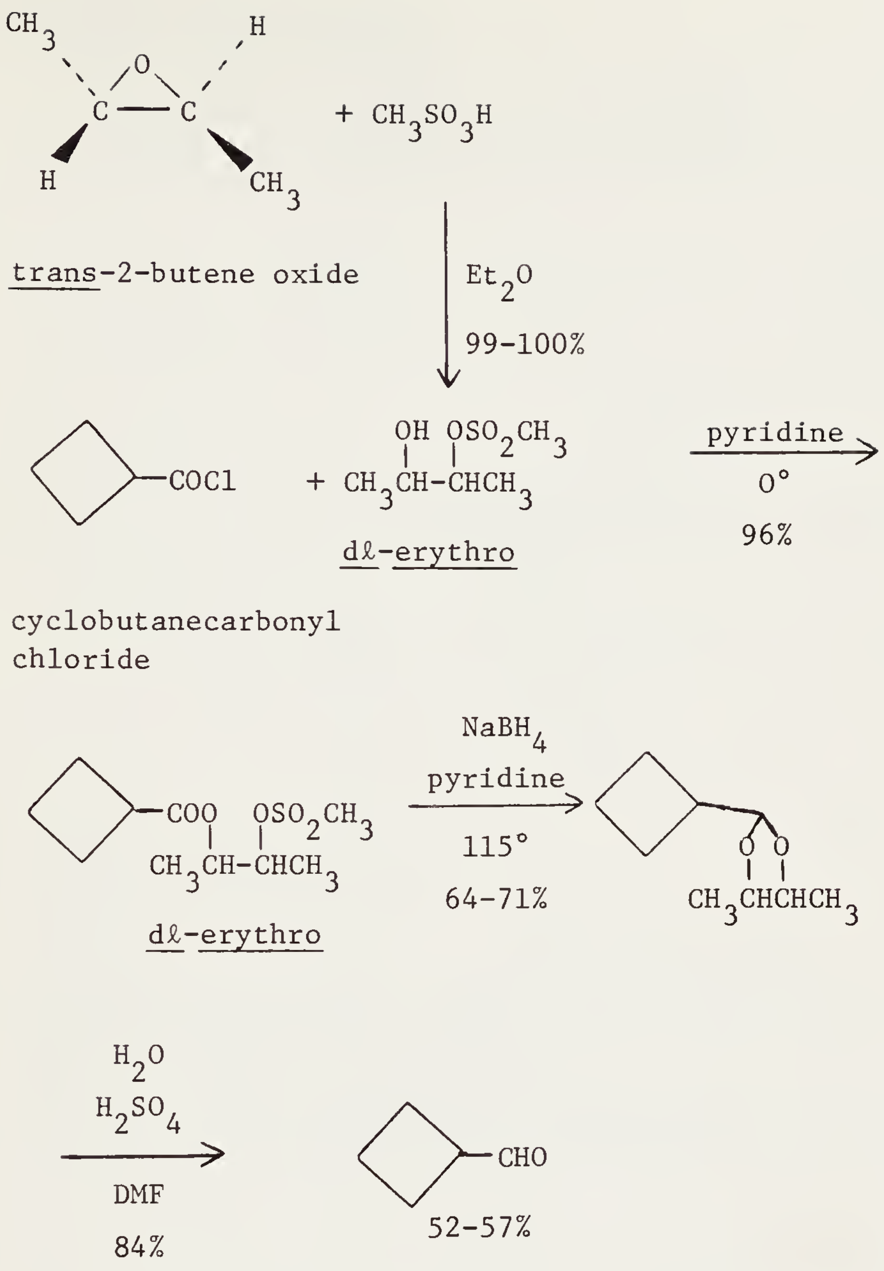


2-benzyl-5,6-dihydro-4,4,6-trimethyl-1,3(4H)-oxazine

1. n-BuLi THF
2. $Br(CH_2)_4Br$
n-BuLi
90-95%
$NaBH_4$
91-99%
$(COOH)_2$
H_2O
75-80%
61-75%

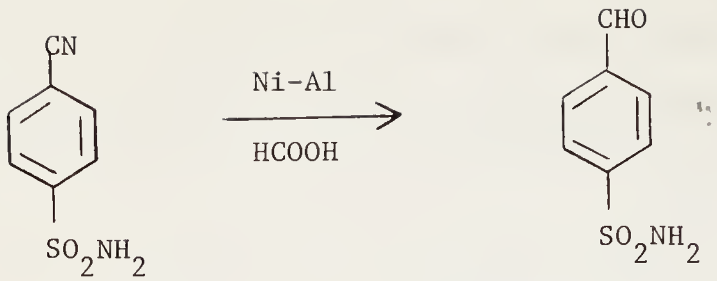
(Mar70-1) Cyclobutanecarboxaldehyde

M. Ross Johnson and Bruce Rickborn, University of California, Santa Barbara, Calif. 93106


trans-2-butene oxide
$+ CH_3SO_3H$
Et_2O
99-100%
cyclobutanecarbonyl chloride
dℓ-erythro
pyridine
0°
96%
$NaBH_4$
pyridine
115°
64-71%
dℓ-erythro
H_2O
H_2SO_4
DMF
84%
52-57%

(Mar70-2) p-Formylbenzenesulfonamide

T. van Es and B. Staskun, University of Witwatersrand,
Johannesburg, South Africa

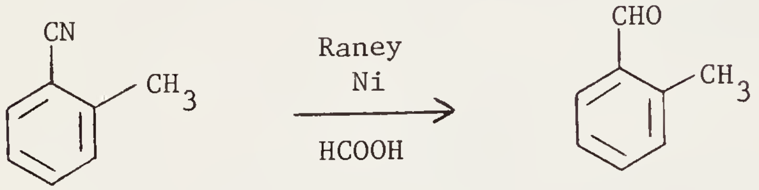

CN
SO2NH2
Ni-Al
HCOOH
CHO
SO2NH2

p-cyanobenzene-sulfonamide

60-70%

(Mar70-3) o-Tolualdehyde

B. Staskun and O. G. Backeberg, University of Witwatersrand, Johannesburg, South Africa


CN
CH3
Raney
Ni
HCOOH
CHO
CH3

o-tolunitrile

70%

(Mar 70-4) n-Octyloxypropanal

Andrée Gaiffe and M. Claude Launay, Laboratoire de Chimie Organique Appliquée, 11, Rue Pierre-Curie, Paris Ve,France

$$CH_3(CH_2)_7OH + CH_2{=}CHCN \xrightarrow{Na} CH_3(CH_2)_7O(CH_2)_2CN$$

1-octanol

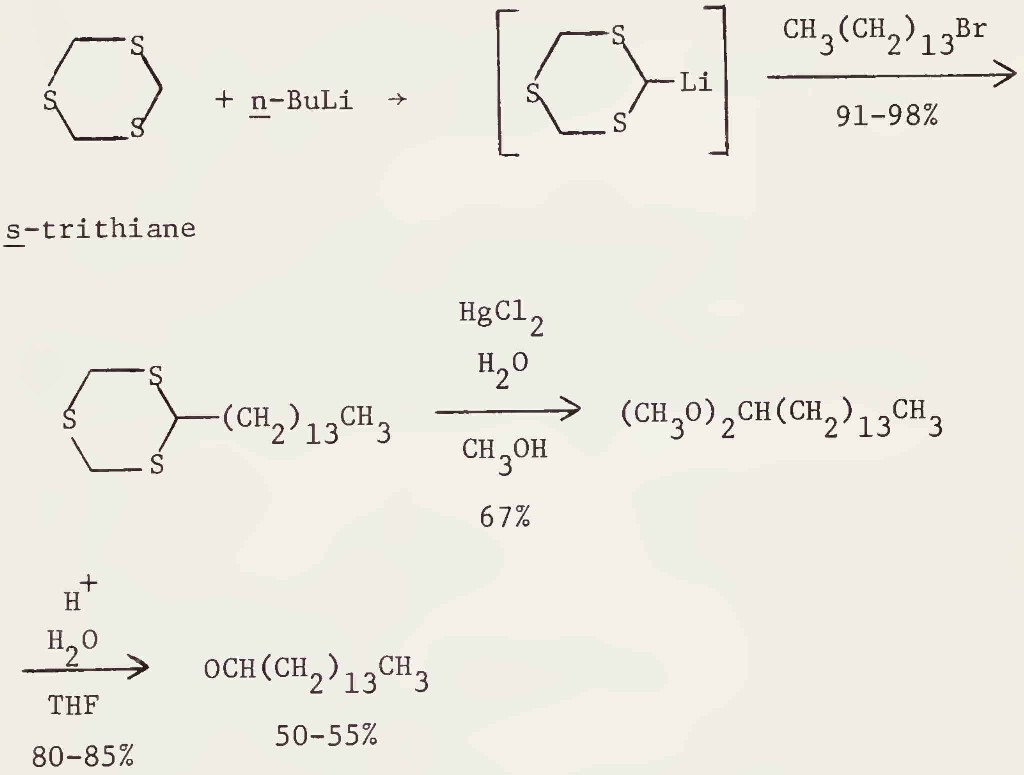
$$\xrightarrow[H_2NNHCONH_2]{\substack{H_2 \\ \text{Raney Ni}}} CH_3(CH_2)_7O(CH_2)_2CH{=}NNHCONH_2$$

$$\xrightarrow{HCHO} CH_3(CH_2)_7O(CH_2)_2CHO$$

27%

(Mar70-5) *n*-Pentadecanal

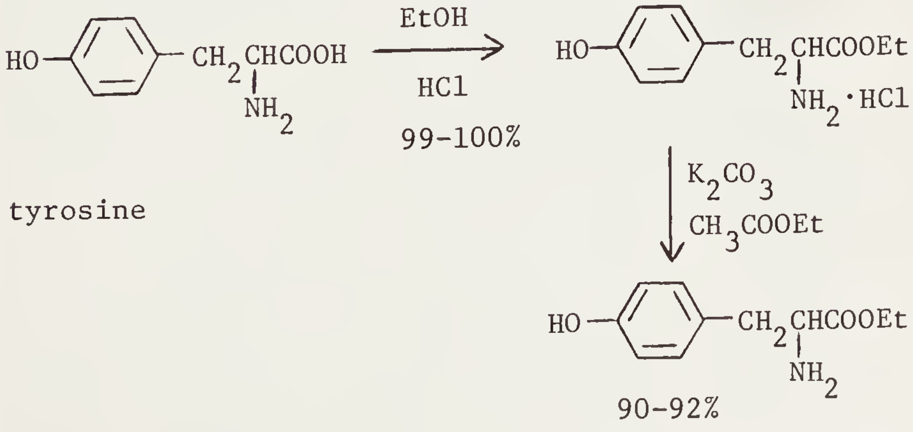
D. Seebach and A. K. Beck, Institut für Organische Chemie der Universität (T.H.), 7500 Karlsruhe, West Germany


+ n-BuLi
Li
$CH_3(CH_2)_{13}Br$
91-98%
$(CH_2)_{13}CH_3$
$HgCl_2$
H_2O
CH_3OH
67%
$(CH_3O)_2CH(CH_2)_{13}CH_3$
H^+
H_2O
THF
80-85%
$OCH(CH_2)_{13}CH_3$
50-55%

s-trithiane

(Mar70-6) Tyrosine Ethyl Ester

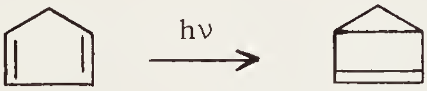
M. Dymicky, E. F. Mellon, and J. Naghski, U. S. Department of Agriculture, 600 East Mermaid Lane, Philadelphia, Pa. 19118


HO
$CH_2CHCOOH$
NH_2
EtOH
HCl
99-100%
$CH_2CHCOOEt$
$NH_2 \cdot HCl$
K_2CO_3
CH_3COOEt
NH_2
90-92%

tyrosine

(May70-1) Bicyclo[2.1.0]pent-2-ene

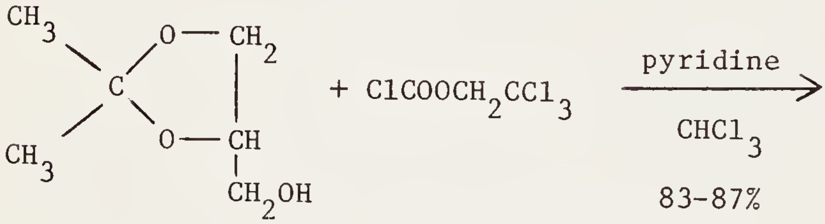
A. Harry Andrist, John E. Baldwin, and Robert K. Pinschmidt, Jr., University of Oregon, Eugene, Oregon 97403



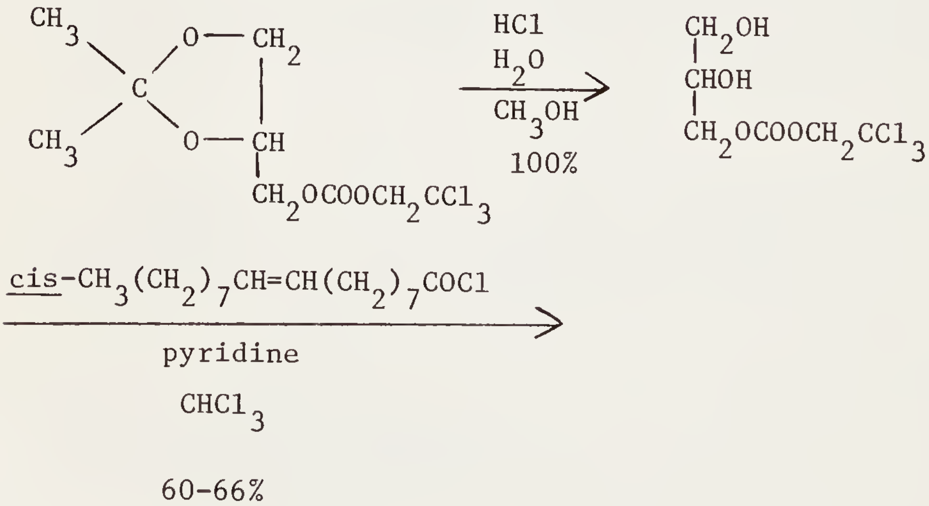
cyclopentadiene

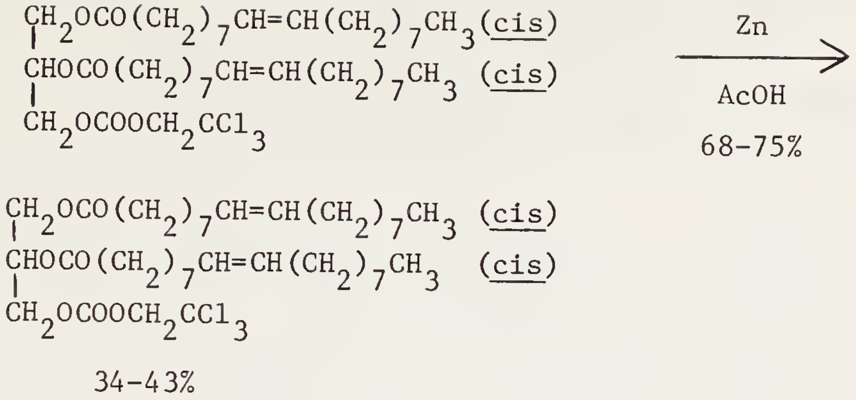
(May70-2) 1,2-Diacyl-*sn*-glycerols

Francis R. Pfeiffer, Clara K. Miao, and Jerry A. Weisbach, Smith Kline and French Laboratories, Philadelphia, Pa.19101


CH_3
CH_3
C
O
O
CH_2
CH
CH_2OH
+ $ClCOOCH_2CCl_3$
pyridine
$CHCl_3$
83-87%

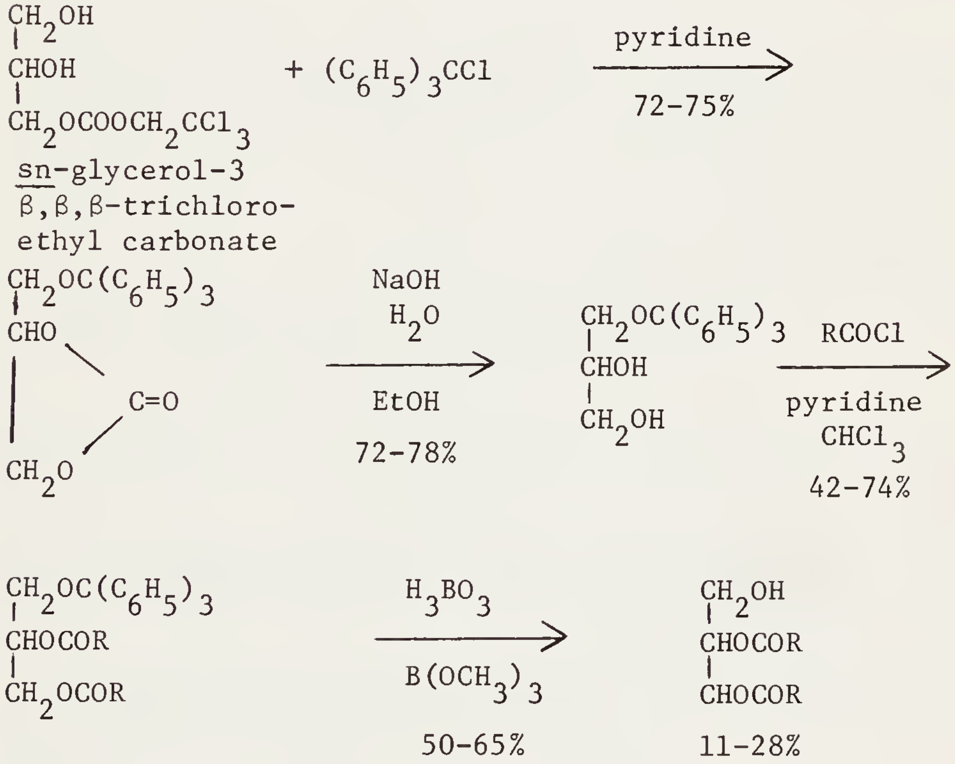
1,2-isopropylidene-*sn*-glycerol


CH_3
CH_3
C
O
O
CH_2
CH
$CH_2OCOOCH_2CCl_3$
HCl
H_2O
CH_3OH
100%
CH_2OH
CHOH
$CH_2OCOOCH_2CCl_3$
cis-$CH_3(CH_2)_7CH{=}CH(CH_2)_7COCl$
pyridine
$CHCl_3$
60-66%


Zn
AcOH
68-75%
(cis)
(cis)
34-43%

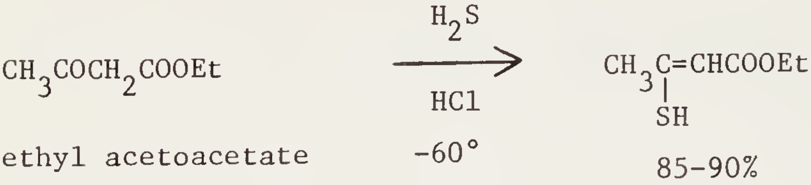
(May70-3) 2,3-Diacyl-*sn*-glycerols

Francis R. Pfeiffer and Jerry A. Weisbach, Smith Kline and French Laboratories, Philadelphia, Pa. 19101


sn-glycerol-3 β,β,β-trichloroethyl carbonate
pyridine
72-75%
NaOH
H2O
EtOH
72-78%
RCOCl
pyridine
CHCl3
42-74%
H3BO3
B(OCH3)3
50-65%
11-28%

(May70-4) Ethyl 3-Mercaptocrotonate

B. Hedegaard, F. Duus, and S.-O. Lawesson, Aarhus University, 8000 Aarhus C, Denmark

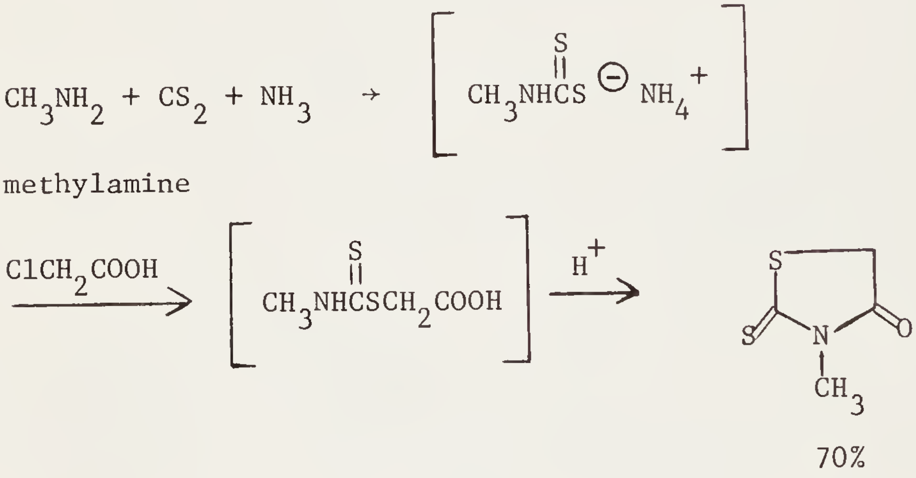


$$CH_3COCH_2COOEt \xrightarrow[\text{HCl}]{H_2S} CH_3C(SH)=CHCOOEt$$

ethyl acetoacetate -60° 85-90%

(Jun70-1) N-Alkylrhodanines. N-Methylrodanine

F. E. Condon, D. G. Shapiro, P. Sulewski, I. G. Vasi, and R. Waldman, The City College of the City University of New York, New York, N. Y. 10031



$$CH_3NH_2 + CS_2 + NH_3 \rightarrow \left[CH_3NH\overset{S}{\overset{\parallel}{C}}S^{\ominus}\ NH_4^+ \right]$$

methylamine

$$\xrightarrow{ClCH_2COOH} \left[CH_3NH\overset{S}{\overset{\parallel}{C}}SCH_2COOH \right] \xrightarrow{H^+}$$

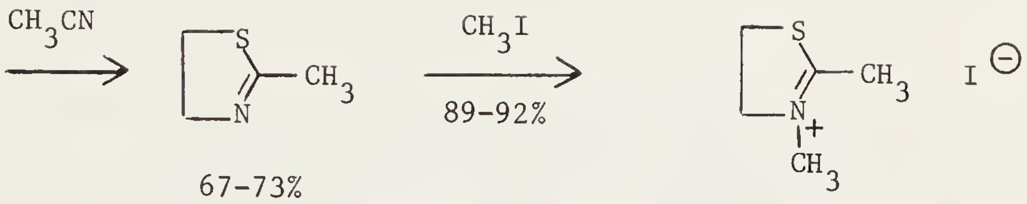
70%

(Jun70-2) 2-Methylthiazoline and 2-Methylthiazoline Methiodide

F. E. Condon and J. P. Trivedi, The City College of the City University of New York, New York, N. Y. 10031

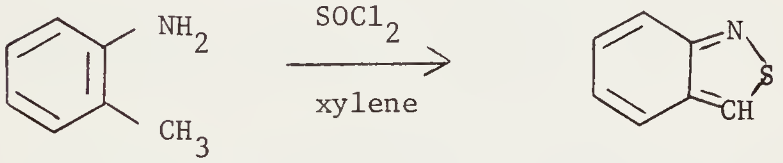
$$HSCH_2CH_2NH_2 \cdot HCl + EtONa \rightarrow [HSCH_2CH_2NH_2]$$

cysteamine hydrochloride


CH3CN
S
N
CH3
67-73%
CH3I
89-92%
S
N
+
CH3
CH3
I ⊖

(Jun70-3) 2,1-Benzisothiazole (Thioanthranil)

Michael Davis and Enno Homfeld, La Trobe University,
Bundoora, Victoria, 3083, Australia

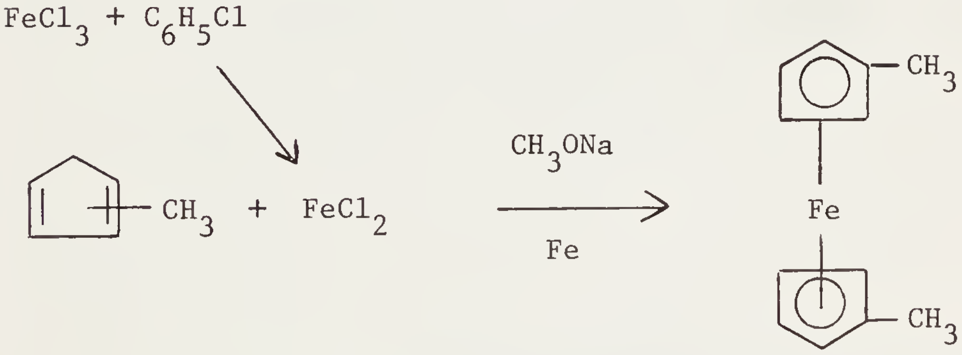

NH2
CH3
SOCl2
xylene
N
S
CH

o-toluidine

13-16%

(Jun70-4) Ferrocenes from Cyclopentadienes: 1,1'-Dimethylferrocene

Ilgvars J. Spilners and Robert J. Hartle, Gulf Research
and Development Co., P.O. Drawer 2038, Pittsburgh, Pa.
15230

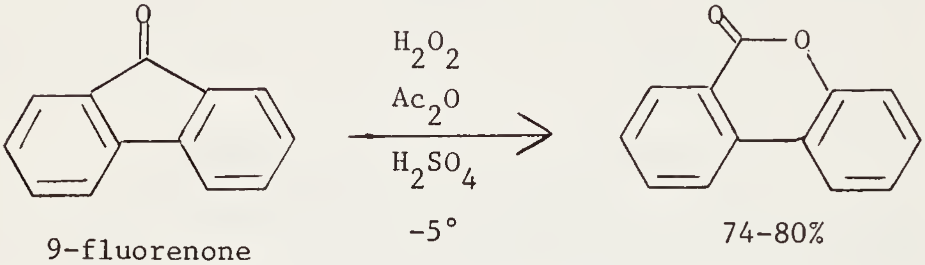

FeCl3 + C6H5Cl
CH3
+
FeCl2
CH3ONa
Fe
CH3
Fe
CH3

methylcyclopentadiene

96%

(Jun70-5) 2'-Hydroxybiphenyl-2-carboxylic Acid Lactone

Alex Gringauz and Eugene Tosk, Brooklyn College of Pharmacy, Long Island University, Brooklyn, N. Y. 11216



9-fluorenone

(Jun70-6) 1-d-2-Methylbutanal

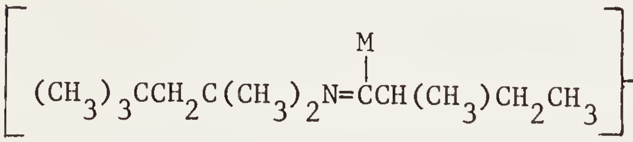
G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, The Florida State University, Tallahassee, Fla. 32306

$(CH_3)_3CCH_2C(CH_3)_2NHCHO \xrightarrow[DMF]{SOCl_2}$

87%

N-(1,1,3,3-tetramethylbutylformamide

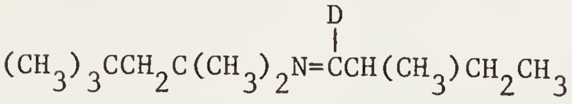
$(CH_3)_3CCH_2C(CH_3)_2NC \xrightarrow[M=Li,\ MgBr]{MCH(CH_3)CH_2CH_3}$



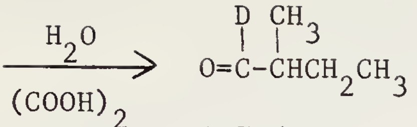
$\left[(CH_3)_3CCH_2C(CH_3)_2N{=}\overset{M}{\overset{|}{C}}CH(CH_3)CH_2CH_3\right] \xrightarrow{D_2O}$

93% (Li)

67% (MgBr)



$(CH_3)_3CCH_2C(CH_3)_2N{=}\overset{D}{\overset{|}{C}}CH(CH_3)CH_2CH_3$



$$\xrightarrow[(COOH)_2]{H_2O} O{=}\overset{D}{\overset{|}{C}}{-}\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$$

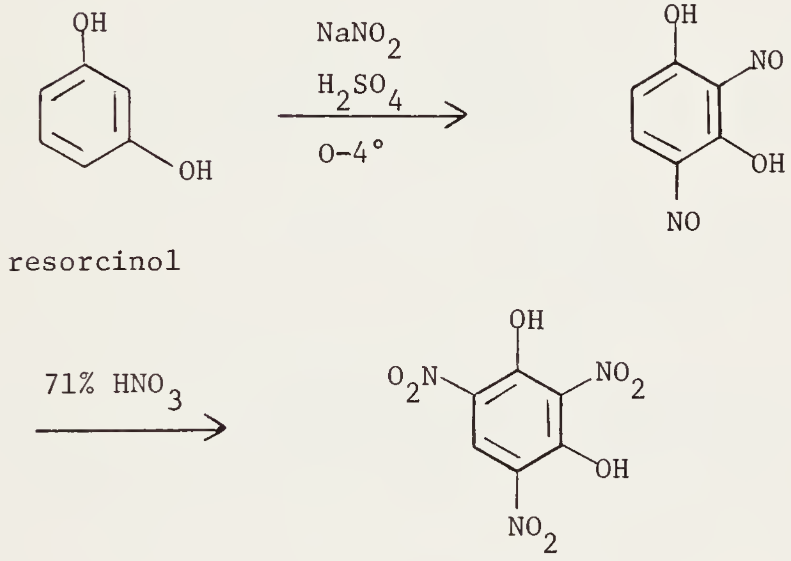
99%

80% (with M=Li)

58% (with M=MgBr)

(Jun70-7) 2,4,6-Trinitroresorcinol (Styphnic Acid)

B. A. Bydal, 1504 Mulberry Rd., Martinsville, Va. 24112


OH
OH
NaNO2
H2SO4
0-4°
OH
NO
OH
NO
71% HNO3
OH
O2N
NO2
OH
NO2

resorcinol

84%

(Jul70-1) Benzoylacetanilide

M. I. Ali, M. A. Abou-State, and A. S. A. Shawali,
Chemistry Department, Faculty of Science, University of
Cairo, Cairo, United Arab Republic

$$C_6H_5COCH_2COOEt + C_6H_5NH_2 \xrightarrow{150\text{-}160°} C_6H_5COCH_2CONHC_6H_5$$

75-77%

ethyl benzoylacetate

(Jul70-2) 2-*t*-Butyl-1,3-diaminopropane

R. O. Hutchins and B. E. Maryanoff, Drexel University,
Philadelphia, Pa. 19104

$$\underset{\text{malononitrile}}{CH_2(CN)_2} + (CH_3)_3CCl \xrightarrow[CH_3NO_2]{AlCl_3}$$

63-68%

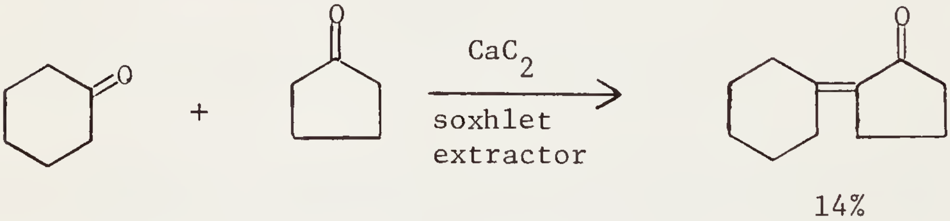
$$(CH_3)_3CCH(CN)_2 \xrightarrow[\text{2. HCl}]{\text{1. } B_2H_6 \text{ THF}} [(CH_3)_3CCH(CH_2NH_2 \cdot HCl)_2]$$

$$\xrightarrow[43\text{-}48\%]{NaOH} (CH_3)_3CCH(CH_2NH_2)_2$$

27-32%

(Jul70-3) 2-Cyclohexylidenecyclopentanone

Richard D. Sands, Alfred University, Alfred, N. Y. 14802



cyclohexanone

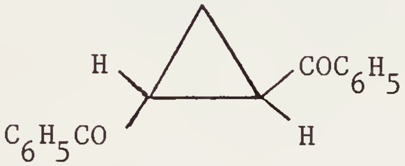
cyclo-
pentanone

(Jul70-4) 1,2-Diaroylcyclopropanes: *trans*-1,2-Dibenzoylcyclopropane

Ismael Colon, Gary W. Griffin, and E. J. O'Connell, Jr., Fairfield University, Fairfield, Conn.

$$C_6H_5CO(CH_2)_3COC_6H_5 + I_2 \xrightarrow[CH_3OH]{NaOH}$$

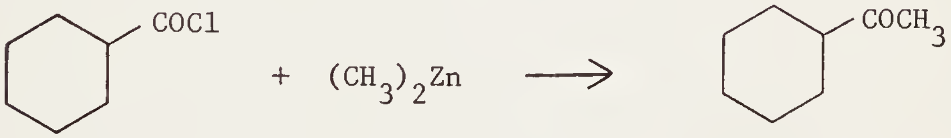
1,3-dibenzoylpropane



66-72%

(Jul70-5) Cyclohexyl Methyl Ketone

Kenneth B. Wiberg, Gary N. Taylor, and George T. Burgmaier, Yale University, New Haven, Conn.

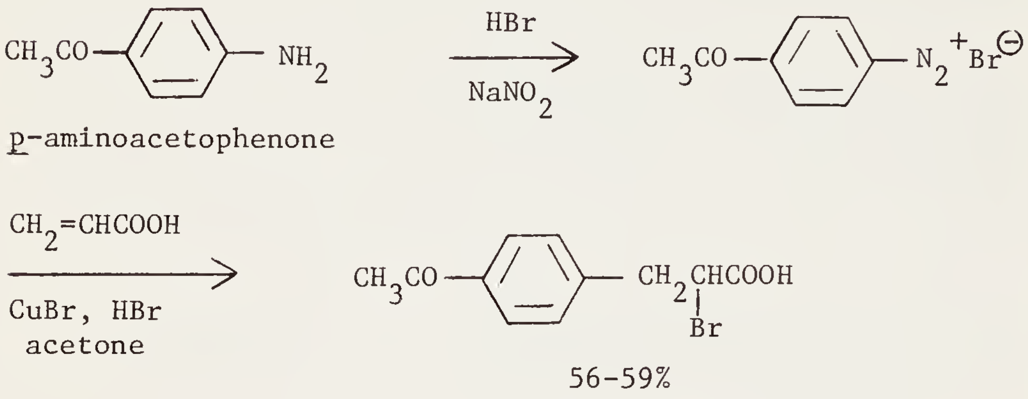


cyclohexanecarbonyl chloride

73-77%

(Jul70-6) p-Acetyl-α-bromohydrocinnamic Acid

George H. Cleland, Occidental College, Los Angeles, Calif.
90041


CH3CO
NH2
HBr
NaNO2
CH3CO
N2+Br⊖
CH2=CHCOOH
CuBr, HBr
acetone
CH3CO
CH2CHCOOH
Br
56-59%

p-aminoacetophenone

Date D

DATE DUE / DATE DE RETOUR

CARR McLEAN

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